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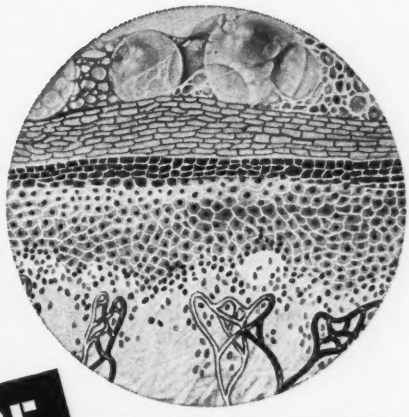

# HANDLE WITH CARE

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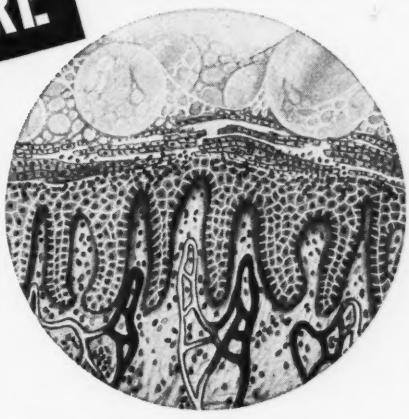

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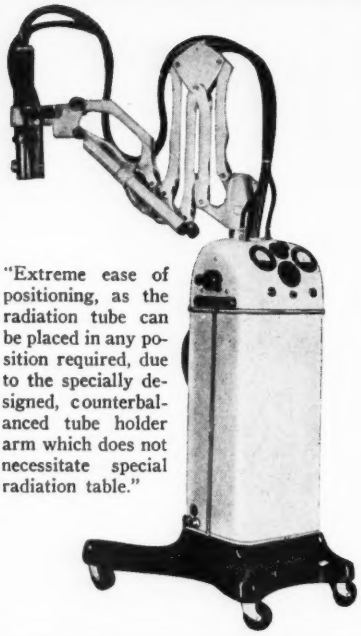

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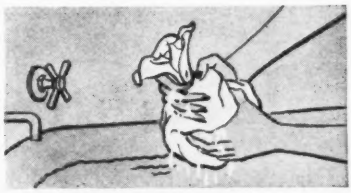

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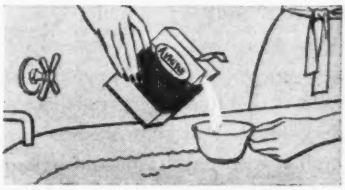

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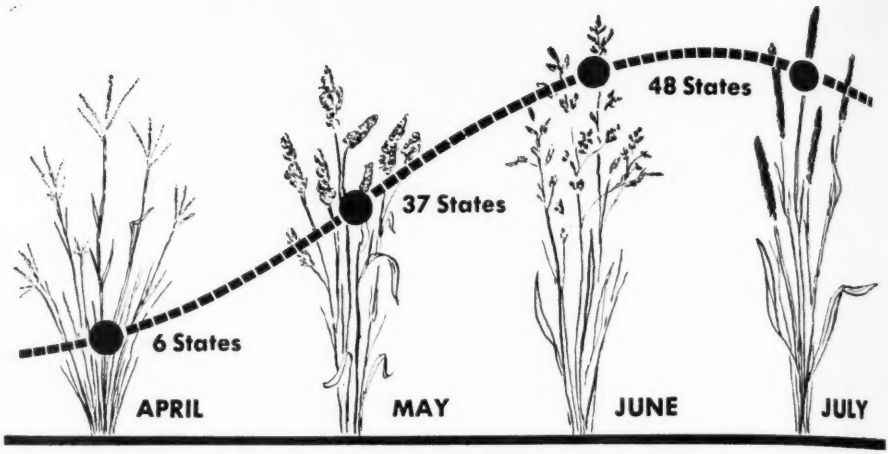


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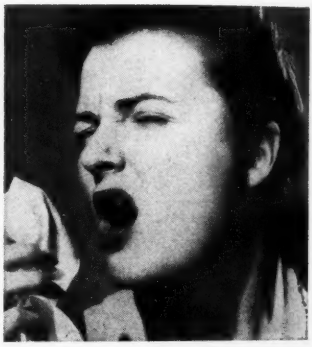

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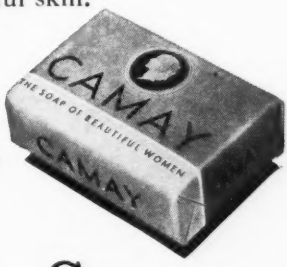


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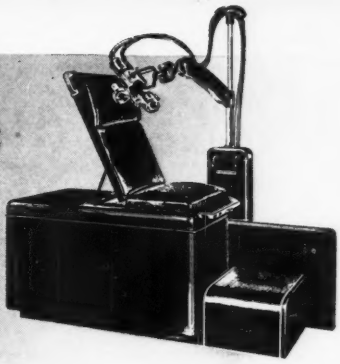

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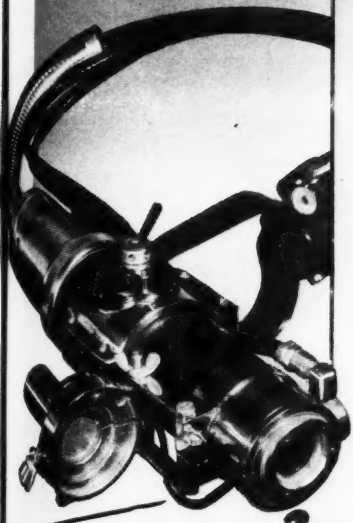

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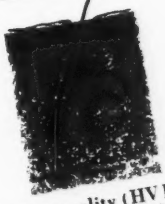

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Archives of Dermatology and Syphilology

VOLUME 61 JUNE 1950 NUMBER 6

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## SYMPOSIUM ON LUPUS ERYTHEMATOSUS

### Including Recent Developments in Diagnosis and Treatment

# LUPUS ERYTHEMATOSUS

### Introduction to the Subject

HENRY SILVER, M.D.
NEW YORK

LUPUS erythematosus has baffled and eluded the medical profession for over one hundred years. The first half of this period has been devoted mainly to the study of the various types of the disease. Kaposi recognized early that the condition is associated with constitutional symptoms. At the turn of the century Jadassohn called attention to the acute type of lupus erythematosus as a serious systemic disease. In recent years Libman and Sachs widened the conception of the syndrome. Their well studied cases, associated with visceral manifestations, especially indeterminate endocarditis, were later identified by Libman as of subacute lupus erythematosus. Careful studies by the Mount Sinai group and the Mayo Clinic group further amplified knowledge of the nature of the disease. Klemperer and Baehr stressed the collagenous changes as evidenced by fibrinoid degeneration.

For purposes of orientation in the present symposium we shall adhere to the accepted classification, which embraces four types: (1) acute disseminated lupus erythematosus, (2) subacute disseminated lupus erythematosus, (3) chronic disseminated lupus erythematosus and (4) chronic discoid lupus erythematosus. A distinction should be made between the disseminated varieties, which usually show evidence of systemic involvement and not necessarily characteristic lesions, and the localized variety, which has no demonstrable systemic disturbances but has characteristic cutaneous manifestations.

While knowledge of the disease in its clinical aspects has been fully established for many years, there has been little advance in the knowledge of etiology, pathogenesis or satisfactory therapy. The proposals of a tuberculous etiology, advanced by European investigators, have not been accepted in spite of cycles of enthusiasm. Many speculative theories led nowhere.

This paper is the first in a "Symposium on Lupus Erythematosus," held at the Bronx Dermatological Society on Dec. 15, 1949.

In the constant search for aid, the dermatologist has turned to the basic sciences in the hope that a clue may come from the borderline fields. Indeed, in recent years there have been many new developments and advances in diagnosis and treatment of lupus erythematosus which merit presentation at this time.

The presentation will be in two groups: The first will cover investigations and recent developments with reference to the hematology, cytology, physiology, histopathology (in connection with which the newer histochemical stains will be stressed), chemistry and serology of the disease. The second will cover the field of therapy and embrace comments on both the older, widely used drugs, such as gold preparations, and the more recently recommended remedies: sodium paraaminobenzoate, bismuth preparations, tocopherols, calciferol, antibiotics, cortisone and ACTH and other steroids.

290 West End Avenue.

# BLOOD FACTOR IN ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS

JOHN R. HASERICK, M.D.
CLEVELAND

THE BLOOD of patients with acute disseminated lupus erythematosus has been found to contain a factor which can be detected by adding the whole plasma of these patients to preparations of human or dog bone marrow. This presentation is concerned with the detection of the "L. E. factor," with its disappearance during complete remissions of the disease and with its identification or association with the gamma globulin fraction of the plasma.

Study of the bone marrow was introduced as an investigative field in acute disseminated lupus erythematosus by work originally done at the special hematology laboratory of the Mayo Clinic. Richmond [1] detected a phenomenon of phagocytosis in the bone marrow of a man who was extremely ill with an undetermined disease. Characteristic of this phenomenon was the cell, which she called the "tart cell." This cell is a polymorphonuclear leukocyte which contains a small inclusion. Hargraves [1] found a similar phenomenon of phagocytosis in patients with acute disseminated lupus erythematosus. He described leukocytic clumping and the so-called "L. E. cell," the latter being similar to the tart cell except that the inclusion was larger, was smoky and homogenized and was apparently of nucleoprotein origin.

In February 1949, at the Cleveland Clinic, my associates and I found that the L. E. phenomenon as described by Hargraves could be readily induced by simply adding the whole plasma of a patient acutely ill with disseminated lupus erythematosus to the bone marrow preparation of any normal person.[2] We utilized the bone marrow as it was aspirated day by day in the special hematology laboratory for the study of various hematologic conditions. Only the highly cellular marrows of lymphatic

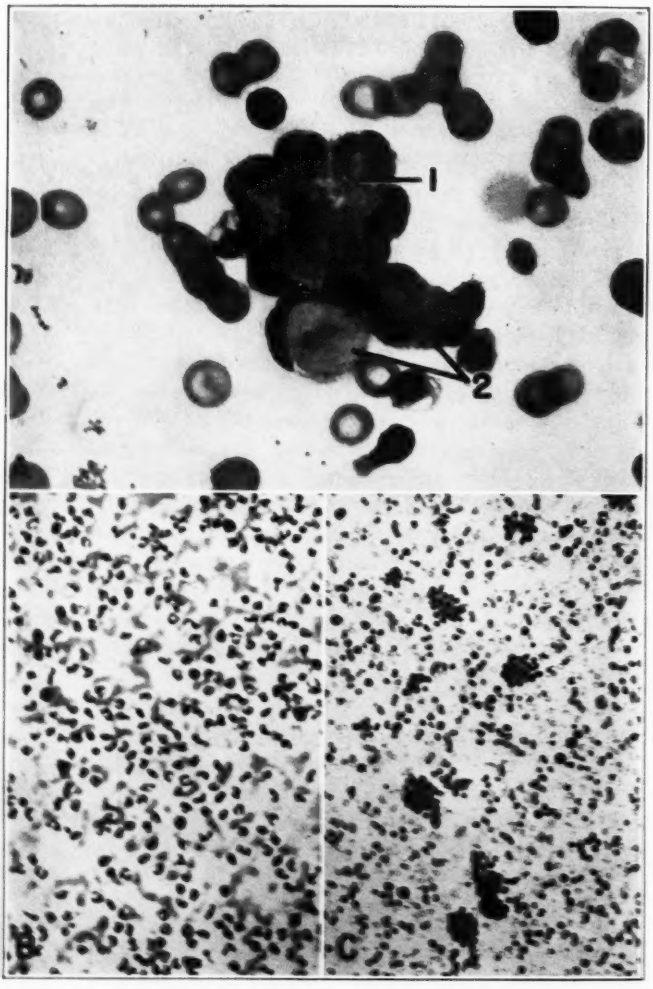
From the Department of Dermatology, Cleveland Clinic.

This paper is the second in a "Symposium on Lupus Erythematosus," held at the Bronx Dermatological Society on Dec. 15, 1949.

1. Hargraves, M. M.; Richmond, H., and Morton, R.: Presentation of Two Bone Marrow Elements: The "Tart" Cell and the "L. E." Cell, Proc. Staff Meet., Mayo Clin. **23**:25-28, 1948.

2. Haserick, J. R. and Bortz, D. W.: Normal Bone Marrow Inclusion Phenomenon Induced by Lupus Erythematosus Plasma, J. Invest. Dermat. **13**: 47-49 (Aug.) 1949.

or monocytic leukemia were found to render the procedure difficult. The addition of plasma from patients with disseminated lupus erythematosus to other bone marrow preparations induced leukocytic clumping and




*A*, normal human marrow after the addition of plasma from a patient with acute disseminated lupus erythematosus; a rosette of leukocytes may be seen at *1*, and L. E. cells, at *2*. *B*, normal dog marrow. *C*, same dog marrow after addition of plasma from a patient with acute disseminated lupus erythematosus.

L. E. cells, both of which have been considered stages of the so-called L. E. phenomenon.

It was found that by adding plasma from patients with disseminated lupus erythematosus to the buffy white cell layer of bone marrow and then making smears from this mixture at 60 second intervals the leukocytic clumping would occur in between five and six minutes and the L. E. cell would appear after twelve or thirteen minutes. Thus the L. E. cell seemed to be merely the end result of the clumping of leukocytes around an amorphous mass of nucleoprotein.

Then, the bone marrow being used as an indicator of the presence of the "L. E. factor" in any given plasma, specimens from patients with several diseases were tested to establish the specificity of the procedure. The L. E. factor was found without exception in 23 cases of acute disseminated lupus erythematosus. It was found to be absent in 2 cases during a remission. It disappeared in a third patient after treatment with cortisone. In subacute and chronic lupus erythematosus, rheumatic fever, rheumatoid arthritis, cirrhosis, scleroderma, dermatomyositis, periarteritis nodosa and several other conditions it was also absent.

The L. E. factor was found to be stable if the plasma was kept sterile. Whole plasma which had been stored for six months under sterile conditions still contained the L. E. factor. On bacterial invasion, however, the L. E. factor was apparently destroyed. Heating of the plasma to 65 C. destroyed it. The factor was inhibited by the addition of paraaminobenzoic acid and by "L. E. antibodies" developed in rabbits. It was not inhibited by cortisone, testosterone, estradiol, progesterone, control antibodies developed in rabbits against plasma or chronic lupus erythematosus plasma. The inhibition by the paraaminobenzoic acid may have been due to a direct attack on the bone marrow cells rather than on the L. E. factor itself.

Fractionations of the whole plasma on the Tiselius electrophoretic apparatus were done on 5 patients with acute disseminated lupus erythematosus. Only the gamma globulin fraction, when added to bone marrow preparations, induced the L. E. phenomenon as whole plasma did. The albumin, alpha and beta globulin fractions induced no alteration when added to bone marrows.

To summarize, these studies indicate the presence of a factor in the blood of patients with acute disseminated lupus erythematosus. This factor is absent during remissions of the disease and is not found in other related conditions. It can be detected, at present at least, only by use of bone marrow preparations. The factor is closely related to the gamma globulin fraction, is stable for long periods when sterile and not overheated and is inhibited by antibodies developed in rabbits against the gamma globulin of the plasma of patients with acute disseminated lupus erythematosus. The procedure of its detection serves as a diagnostic aid and promises to be of value as an investigative procedure.

Department of Dermatology, Cleveland Clinic.

# DEPOLYMERIZATION OF NUCLEIC ACID IN ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS

BORIS GUEFT, M.D.*
NEW YORK

THE PURPOSE of this presentation is to refer to a previously noted structural alteration that has been observed in lupus erythematosus and to emphasize its significance, which has become evident only after cytochemical analysis.

In 1932 Gross [1] reported the presence of "clumps and packets of hematoxylin staining bodies" in the cardiac lesions (fig. 1) of Libman-Sacks disease, later identified with acute lupus erythematosus. He expressed the conclusion that these masses originated in nuclear material and that they were pathognomonic. In 1940, Ginzler and Fox [2] found similar masses in necrotic lymph nodes in this disease (fig. 2). They also described basophilic particles in the glomerular loops of the kidney, which observation was confirmed in 1941 by Klemperer, Pollack and Baehr.[3]

In the past two years my associates and I have observed 4 cases of acute lupus erythematosus in which the same hematoxylin-staining masses were found in many different sites, including the heart, lymph nodes, kidney, lung and spleen—always in tissues of mesenchymal origin. They were sometimes found as the huge aggregated masses described by Gross and by Ginzler and Fox, and at other times in single cell–sized masses to be described later. This observation necessitated a reexamination of the collected material. In 31 of 34 collected cases studied these "hematoxylin-stained bodies" were seen. In 19 of these 34 cases the bodies were present in two or more different sites. In some of the cases most striking generalized changes of this type were observed. In additional recent cases these bodies were present in numerous sites.

---

* Welt Fellow in Pathology, Mount Sinai Hospital.

This paper is the third in a "Symposium on Lupus Erythematosus," held at the Bronx Dermatological Society on Dec. 15, 1950.

1. Gross, L., in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman, New York, International Press, 1932, vol. 2, p. 527.

2. Ginzler, A. M., and Fox, T. T.: Disseminated Lupus Erythematosus: Cutaneous Manifestation of Systemic Disease (Libman-Sacks); Report of Case, Arch. Int. Med. **65**:26-50 (Jan.) 1940.

3. Klemperer, P.; Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. **37**:569-631 (Oct.) 1941. Klemperer, P.: Ann. Int. Med. **28**:1-11, 1948.

The most commonly affected organs were the kidneys and the endocardium. Therefore, large numbers of control hearts and kidneys were searched for these bodies. The control cases included cases of rheumatic and bacterial endocarditis, diffuse and focal glomerulonephritis, malignant nephrosclerosis and periarteritis nodosa. In none of these control cases were hematoxylin-stained bodies found.

The hematoxylin-stained bodies are similar wherever found. In sections stained with hematoxylin and eosin they are red-purple,

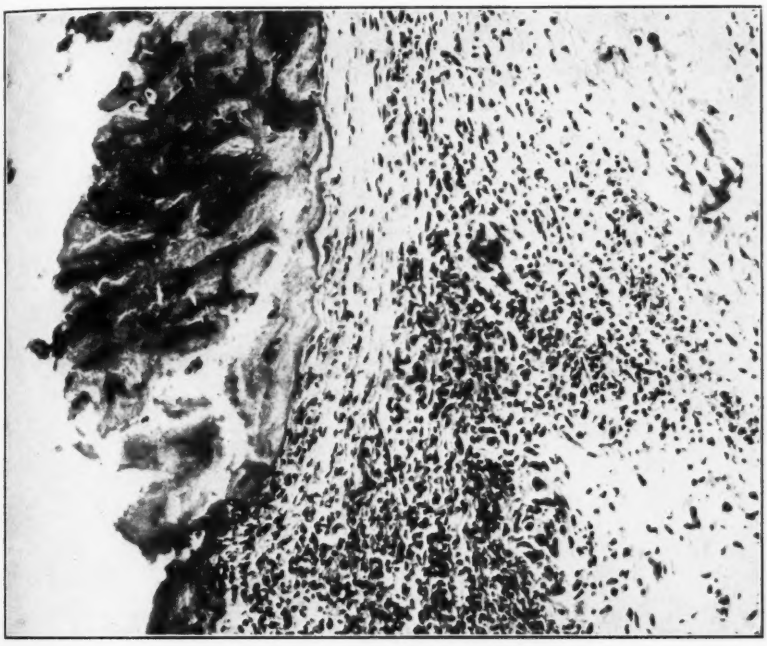


Fig. 1.—Large hematoxylin-stained bodies in vegetations of mitral valve; hematoxylin and eosin, × 150.

homogenous and free of any distinct structures such as chromatin bands or dots (figs. 3 and 4). The single bodies are of cell size, while the larger aggregates are up to several hundred microns in diameter and frequently compose a large portion of a grossly visible structure such as a vegetation of a valve. Their origin from nuclei can be easily traced. If affected, histiocytes, fibroblasts, fibrocytes, lymphocytes, endothelial cells and polymorphonuclear leukocytes show a most striking change in their chromatin, namely homogenization and purple-red staining as

seen in the "free" hematoxylin bodies (those free of cytoplasm). In our material, no cells other than those of mesenchymal origin were found involved. We limited our observation to paraffin sections. Other workers (Hargraves and Haserick and Sundberg [4]) observed peculiar bodies apparently consisting of altered nuclear material in aspirated marrow in acute lupus erythematosus. They expressed the opinion that these peculiar bodies together with their phagocytosing cells are specific for this disease and called the combination "L. E. cells." Our studies [5] indi-

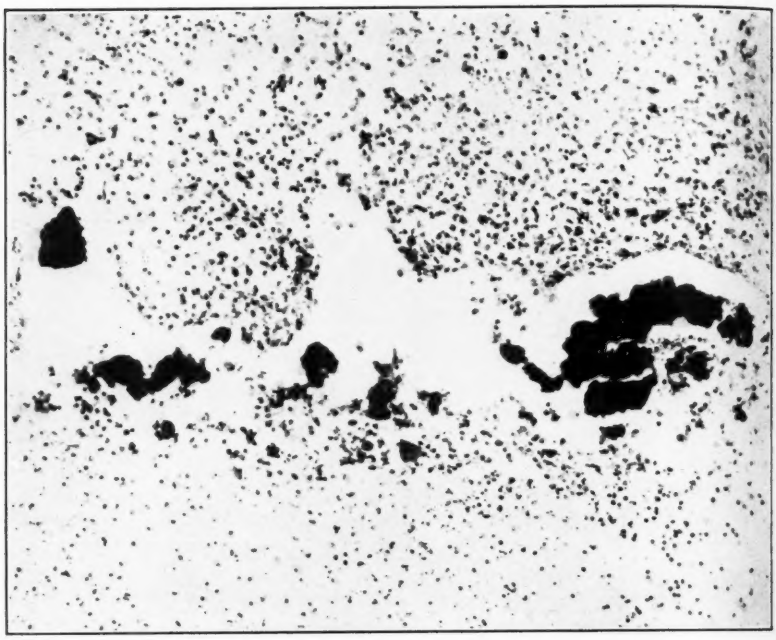


Fig. 2.—Large hematoxylin-stained bodies, in lymph node stained by Feulgen reaction for desoxyribosenucleic acid, × 150.

cated that the phagocytosed material of the L. E. cell is identical with the individual or small hematoxylin-stained bodies previously described. We have even found one L. E. cell at autopsy in a case of acute lupus erythematosus in a routine paraffin section. This rarity suggests that

4. Haserick, J. R., and Sundberg, R. D.: J. Invest. Dermat. **11**:209-213, 1948.

5. Klemperer, P.; Gueft, B.; Lee, S.; Leuchtenberger, C., and Pollister, A. W.: Cytochemical Changes of Acute Lupus Erythematosus, Arch. Path. **49**:503-516 (May) 1950.

the phagocytic action is uncommon in vivo, as the isolated unphagocytosed bodies are relatively numerous in sections.

Histochemical analysis of these bodies was possible only through the assistance and guidance of Dr. A. W. Pollister and Dr. C. Leuchtenberger, of the Department of Zoology, Columbia University, New York. Spectrophotography in the ultraviolet spectrum shows a strong absorption at a wavelength of 2,537 angstrom units. The absorption is lost after treatment of the specimens with hot trichloroacetic acid. Digestion

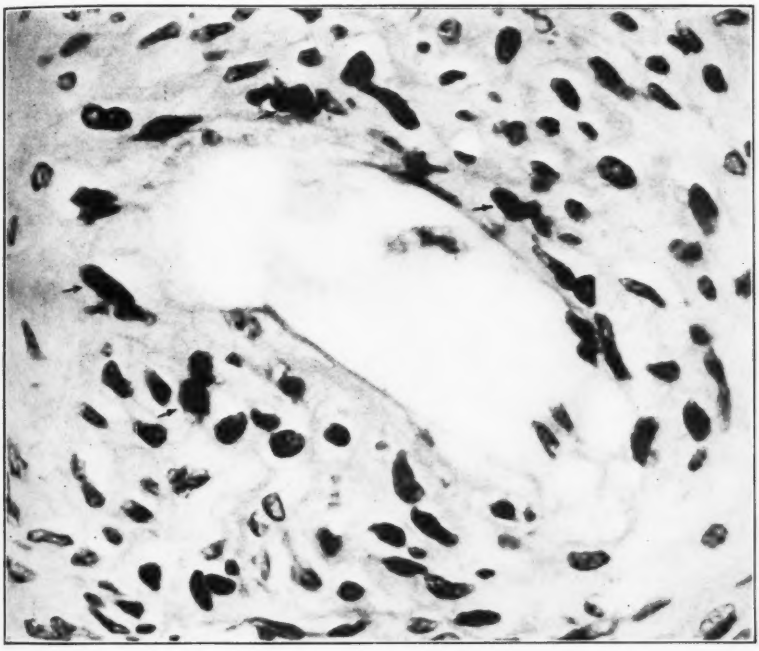


Fig. 3.—Small hematoxylin-stained bodies in perivascular tissue in a grossly normal ovary; hematoxylin and eosin, × 600.

with ribonuclease has no effect, while the Feulgen reaction for desoxyribosenucleic acid is positive (fig. 2). These observations are convincing evidence that the hematoxylin-stained bodies are derived from nuclear chromatin and contain desoxyribosenucleic acid. The bodies also stain weakly with purified methyl green.[6] Pollister and Leuchtenberger

6. The dye is a National Aniline product, color index no. 685, certification no. NG 25, total dye content 93 per cent.

recently demonstrated [7] that the loss of affinity for methyl green together with a relatively strong Feulgen reaction (both reactions measured quantitatively on the Pollister-Moses apparatus) indicates depolymerization of the desoxypentosenucleic acid.

Our observations thus indicate that the nucleic acid of the hematoxylin-stained bodies is in a depolymerized state and that one of the factors in the morbid process of lupus erythematosus is a disturbance of the nucleic acid metabolism manifested as a depolymerization of the desoxyribosenucleic acid.

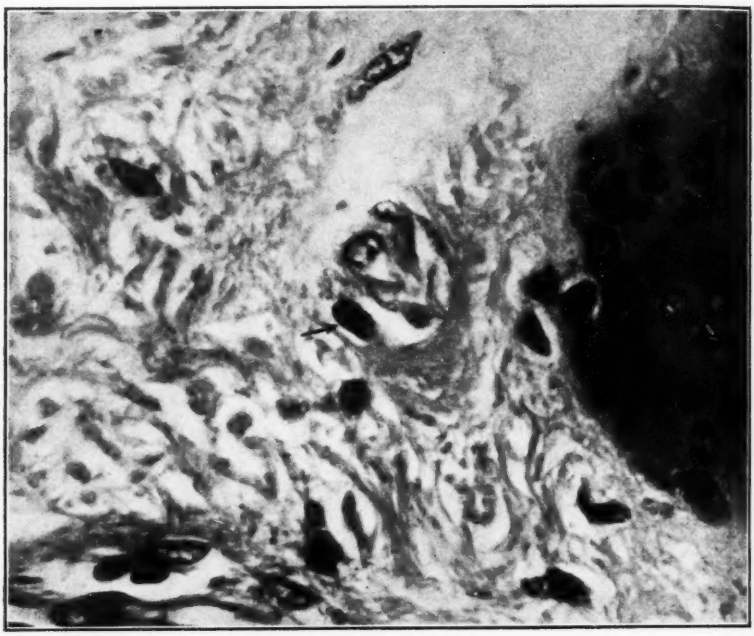


Fig. 4.—Skin, showing an isolated hematoxylin-stained body (arrow) in the wall of an arteriole; hematoxylin and eosin, × 600.

In the past, conspicuous changes of the extracellular portion of the connective tissue were described as occurring in acute lupus erythematosus. These were fibrinoid alteration of the collagen fibers, periarterial fibrosis in the spleen and increase in metachromasia of the loose connective tissue ground substance. These changes have frequently been associated and may be present in a single area. The relation of these

7. Pollister, A. W., and Leuchtenberger, C.: Proc. Nat. Acad. Sc. **35**:111-116, 1949.

previously described extracellular lesions to the changes described herein is unknown. It has been noted that the hematoxylin bodies are frequently found where the most conspicuous connective tissue lesions occur. This suggests an interrelationship of the nuclear depolymerization and the connective tissue lesions or a common supraordinated factor acting on both. Since the fibers and ground substance are doubtless influenced by the condition of their parent cells, one may think that the cellular abnormality described here may account for the abnormality of the fibers and ground substance. Thus one may assume that there is depolymerization of fibroblast nuclei associated with fibrinoid alteration and disintegration of the nearby collagen fibers and an increase in the surrounding ground substance. Perhaps some of the depolymerizing nucleoprotein diffuses into the surrounding milieu and also changes the staining reactions of the components of the connective tissue (fibers and ground substance).

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# LUPUS ERYTHEMATOSUS: SEROLOGIC AND CHEMICAL ASPECTS

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IT IS THE purpose of this paper to discuss the problem of the biologic false positive reactions in the serologic test for syphilis in lupus erythematosus and to report the results of a study of this problem. The serum protein changes in lupus erythematosus will be considered, and their possible relation to the production of biologic false positive reactions will be discussed.

The most complete review of the literature on the problem of the false positive reaction in lupus erythematosus was given by C. J. White [1] in 1947. Gennerich [2] was probably the first to suggest its existence. Keil [3] reported 10 cases of lupus erythematosus with positive reactions in Wassermann tests of the blood and made the statements that reactions to serologic tests may fluctuate widely with different technics and that a high Wassermann titer carried a bad prognosis. In 1 of his cases there was a "paretic" colloidal gold curve with no clinical evidence of syphilis. Coburn and Gutman [2] studied 2 classic examples of lupus erythematosus and expressed the belief that a biologic false positive Wassermann reaction resulted from the disease. Taussig,[2] Keil [3] and Coburn and Gutman [2] expressed the opinion that the factors responsible were in the globulin fraction. Smith [2] reported 1 case and stated agreement with Keil that there is an increase in the globulin fraction in lupus erythematosus. Pillow and Palmer [4] noted 2 cases of

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From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School, Dr. Marion B. Sulzberger, chairman, and the Skin and Cancer Unit of University Hospital.

1. White, C. J.: The Problems of Positive Serologic Tests for Syphilis in Lupus Erythematosus, Am. J. Syph., Gonor. & Ven. Dis. **31**:235 (March) 1947.

2. Cited by White.[1]

3. Keil, H.: Dermatomyositis and Systemic Lupus Erythematosus: Comparative Study of Essential Clinicopathologic Features, Arch. Int. Med. **66**:339 (Aug.) 1940.

4. Pillow, R. P., and Palmer, L. J.: Lupus Erythematosus Disseminatus, Northwest Med. **44**:142 (May) 1945.

lupus erythematosus in 1 of which the reactions to the Kahn and Kolmer tests were repeatedly strongly positive, and in the other of which reactions to both tests were doubtful in two different laboratories.

Sompayrac and Hailey [2] reported a case in which the symptoms of lupus erythematosus occurred before the onset of lesions of the skin. Antisyphilitic treatment was started because the reaction in the serologic test for syphilis was consistently positive, but this therapy was discontinued in less than two weeks because of the onset of new lesions and a flare-up of old lesions on the face. In the course of a few months the reaction in the serologic test for syphilis became negative and remained so.

Coburn and Moore [5] studied 30 patients with disseminated lupus erythematosus, none of whom had evidence of syphilis. Of these, 11 patients had positive Wassermann reactions and 13 showed positive Kline reactions. Of 15 patients with disseminated lupus erythematosus, all showed inversion of the albumin-globulin ratio due to increased globulin and lowered albumin levels. Coburn and Moore concluded that hypergammaglobulinemia is a constant characteristic of disseminated lupus erythematosus and is responsible for false positive Wassermann and Kline reactions. Keil, on the other hand, observed many instances of systemic lupus erythematosus in which there was no elevation in the serum globulin. He concluded that there is no correlation between the serologic phenomena and the globulin values.

Beerman [6] stated that false positive serologic reactions in tests for syphilis in lupus erythematosus are rare and represent technical errors or undiagnosed syphilis. He noted that of Ambrosetti's [7] series of 108 patients with lupus erythematosus only 3.7 per cent had positive reactions. Schaumann and Heden [2] found 2 patients with positive Wassermann reactions among 75 patients with lupus erythematosus. Boas and With [2] found no positive Wassermann reactions in 146 patients with lupus erythematosus. Gougerot and Burnier [2] noted one positive reaction to the serologic test for syphilis among 50 patients with lupus erythematosus. Throne's [2] 36 patients with lupus erythematosus gave negative reactions except 1 person with a history of venereal disease.

Freund [2] reported positive reactions in 9 per cent of 249 patients with lupus erythematosus. Prochazka [2] had 73 cases of lupus erythematosus, in 43.9 per cent of which there was increased anticomplementary capacity. Margarot, Rembaud and Ravoire [2] found positive reactions

5. Coburn, A. F., and Moore, D. H.: The Plasma Proteins in Disseminated Lupus Erythematosus, Bull. Johns Hopkins Hosp. **73**:196 (Sept.) 1943.

6. Beerman, H.: Biologic False Positive Reactions, Am. J. M. Sc. **209**:525 (April) 1945.

7. Ambrosetti, cited by Beerman.[6]

to serologic tests for syphilis in 24 per cent of their cases. Carrera [2] found 30 per cent of patients with lupus erythematosus to have positive reactions. Pessano [2] reported 8.3 per cent with positive reactions in 84 patients with lupus erythematosus.

In the discussion of a paper by Baehr and Pollack, Baehr [8] concluded that the Wassermann reaction is often falsely positive in lupus erythematosus and may fluctuate from negative to falsely positive and back again. He expressed doubt, however, that this was due to the rise in euglobulin, because of the fluctuating variability of the serologic phenomena.

Montgomery and McCreight [9] recently reviewed the cases of lupus erythematosus seen at the Mayo Clinic. Among 154 cases of disseminated lupus erythematosus seen up to 1938, in 6 per cent of the chronic, 11 per cent of the subacute and 17 per cent of the acute cases there were positive reactions to serologic tests for syphilis. In a more recent series of 132 cases of disseminated lupus erythematosus seen between 1938 and 1947, these authors found that in 17 per cent of the chronic, 25 per cent of the subacute and 44 per cent of the acute cases there were positive reactions. The increase in the percentages of false positive serologic tests for syphilis in the later series was attributed to the fact that a battery of four serologic tests was performed, whereas in the earlier series only one or two tests were done. These workers concluded that the incidence of positive reactions in serologic tests for syphilis increases with the severity of the lupus erythematosus.

It is evident then from a review of the literature that widely divergent reports exist regarding the incidence of false positive reactions to serologic tests for syphilis in lupus erythematosus. They range from none, in Boas and With's series, to 44 per cent in Montgomery and McCreight's review of the cases of acute disseminated lupus erythematosus encountered at the Mayo Clinic. In an evaluation of a study on the subject the following factors must be considered: (1) the sensitivity of the tests performed, (2) the number of tests done on each sample of serum, (3) the frequency of repetition of tests and (4) the stage of the disease. Unless these four factors are considered, comparisons are inaccurate.

## RESULTS OF THE PRESENT STUDY

During the past three years we have studied the incidence of biologic false positive reactions in serums of patients with lupus erythema-

8. Baehr, G., in discussion on Baehr, G., and Pollack, A. D.: Disseminated Lupus Erythematosus and Diffuse Scleroderma, J. A. M. A. **134**:1169 (Aug. 2) 1947.

9. Montgomery, H., and McCreight, W. G.: Disseminate Lupus Erythematosus, Arch. Dermat. & Syph. **60**:356 (Sept.) 1949.

tosus. The first part of the study consisted of the examination of serums of patients whose cases were diagnosed as lupus erythematosus, at the Skin and Cancer Unit and from private practice. The second part of the study consisted of the examination of serums of patients with lupus erythematosus which were sent to us by mail in merthiolated test tubes from dermatologic centers throughout the country. Each specimen of serum was subjected to a battery of six serologic tests for syphilis including the Mazzini, Venereal Disease Research Laboratory, Kline exclusion and Rein-Bossak flocculation tests and the Kolmer and cardiolipin complement fixation tests. As far as possible, syphilitic infections were ruled out by history and physical examination.

Of a total of 178 such serums, obtained from 176 patients with lupus erythematosus, 35 per cent gave positive reactions to one or more of the tests in the battery.

In the Skin and Cancer series, 20 per cent of 92 serums examined gave positive reactions. Seventy per cent of the cases in this series were of chronic localized discoid lupus erythematosus; 12 per cent were of chronic disseminated discoid lupus erythematosus and 15 per cent were of subacute disseminated lupus erythematosus. Of the serums of chronic localized discoid lupus erythematosus, 15 per cent gave positive reactions in serologic tests for syphilis; of those of chronic disseminated discoid lupus erythematosus, 18 per cent gave positive reactions, and, of those of the subacute disseminated lupus erythematosus, 36 per cent gave positive reactions. No serums from cases of acute disseminated lupus erythematosus were studied in the Skin and Cancer series.

In the series of serums examined in the field study, of 86, 52 per cent showed positive serologic reactions for syphilis in one or more tests. The breakdown of this series is as follows: chronic localized discoid lupus erythematosus, 57 per cent; chronic disseminated discoid lupus erythematosus, 5 per cent; subacute disseminated lupus erythematosus, 28 per cent, and acute disseminated lupus erythematosus, 8 per cent. Of the serums from cases of chronic localized discoid lupus erythematosus 57 per cent showed positive reactions to tests for syphilis; of the serums of chronic disseminated discoid lupus erythematosus, 75 per cent showed positive reactions; of the serums of subacute disseminated lupus erythematosus, 37.5 per cent showed positive reactions, and of the serums of acute disseminated lupus erythematosus, 43 per cent gave positive reactions in tests for syphilis.

A significant observation in the tests done on the field series was the fact that 83 per cent of the serums showed anticomplementary activity in one or both of the complement fixation tests performed.

In the analysis of the incidence of false positive reactions in serologic tests for syphilis in these series, it should be mentioned that in 83 per

cent of the serums found positive, the titers of positivity were low, ranging from plus minus to 2 plus. When higher titers were obtained, the serums were usually those from cases of subacute disseminated lupus erythematosus.

### SERUM PROTEIN CHANGES IN LUPUS ERYTHEMATOSUS

Many workers in the past recognized the fact that lupus erythematosus is often associated with a rise in the globulin fraction of the serum with a reversal of the albumin-globulin ratio. Coburn and Moore concluded that hypergammaglobulinemia was a constant characteristic of disseminated lupus erythematosus and was responsible for false positive reactions to serologic tests for syphilis. Keil, however, observed many instances of disseminated lupus erythematosus in which the globulin level in the serum was normal. He concluded that there was no correlation between the serologic phenomena and the globulin values. In an analysis of protein changes in the cases of disseminated lupus erythematosus at the Mayo Clinic between 1938 and 1947, Montgomery and McCreight found that in 84 per cent of the cases of subacute disseminated lupus erythematosus and in 94 per cent of the cases of acute disseminated lupus erythematosus there were reversals of the serum albumin-globulin ratios.

A recent study of the electrophoretic patterns of serums of lupus erythematosus was accomplished by Walker and Benditt.[10] These workers observed a tendency toward a drop in serum albumin and a rise in gamma globulin even in chronic discoid lupus erythematosus. In subacute and acute disseminated lupus erythematosus this tendency became more statistically significant. In addition, in acute disseminated lupus erythematosus there was a drop in the beta globulin concentration. No significant change occurred in the total protein value.

### COMMENTS

The high incidence of biologic false positive reactions found in this study as compared with that observed by most other investigators is a reflection of the sensitivity, variety and number of the serologic tests employed. Whereas in the Skin and Cancer study the percentage of positive reactions reflected the activity of the stage of the disease, in the field study there was no relation between the stage of the disease and the incidence of false positive reactions to serologic tests for syphilis. The high percentage of biologic false positive reactions, even in those cases clinically diagnosed as of chronic localized discoid lupus erythematosus, suggests that some systemic disturbance occurs even when the visible

10. Walker, S. A., and Benditt: Personal communication to the authors.

changes are localized to limited areas of the skin. There is some evidence, moreover, that such serologic phenomena may be the first and only sign of lupus erythematosus and may warn of impending clinical activity.

It is evident that the serums of patients with lupus erythematosus in a high percentage of cases contain increased levels of gamma globulin, as well as having increased false positive reactions in tests for syphilis. It is not evident, however, that the former phenomena, i. e., hypergammaglobulinemia, is responsible for the serologic changes. No evidence is yet available that these serums which give positive reactions to tests for syphilis specifically show increased levels of gamma globulin.

## CONCLUSIONS

Serologic tests for syphilis performed on 178 serums of patients with lupus erythematosus revealed an over-all incidence of 35 per cent for biologic false positive reactions in one or more of a battery of six serologic tests for syphilis.

It should be emphasized that 83 per cent of those serums found positive showed low titers of reactivity.

The majority of those serums manifesting higher titers were those of patients with subacute lupus erythematosus.

The high incidence of biologic false positive reactions even in those cases clinically diagnosed as of chronic localized discoid lupus erythematosus, as well as the hypergammaglobulinemia in these cases, suggests the presence of some systemic disturbance even when the visible changes are limited to isolated areas of the skin.

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# LUPUS ERYTHEMATOSUS: PHYSIOLOGIC ASPECTS

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IN A DISEASE, such as lupus erythematosus, for which the etiology is unknown, a great deal of effort becomes directed toward the expansion of knowledge of its hematology, cytology and pathology. It is well not to overlook investigations into the physiologic or functional alterations which occur in this condition, for a clue may come from this direction.

The new staining technics have thrown much light on the pathology of lupus erythematosus. They may also indicate what lies behind this pathology. Altschuler and Angevine of the University of Wisconsin [1] and many others expressed the opinion that the essential feature of fibrinoid degeneration is the precipitation of acid mucopolysaccharide. The compound in this group that has been mentioned most frequently in recent medical literature is hyaluronic acid. This is a large and structurally asymmetric compound which is highly viscous even in low concentrations. The aforementioned authors stated the belief that the most likely mechanism for this precipitation is the combination of the acid mucopolysaccharide with an alkaline protein. Their investigations would seem to support this hypothesis, but much further work is needed to elaborate it.

Functional changes in lupus erythematosus have also been approached from the vascular point of view. At the last meeting of the Society for Investigative Dermatology, Taylor and Huff [2] reported on a study of the peripheral circulation in lupus erythematosus. They compared the vasodilation in the fingers of persons afflicted with lupus erythematosus with that of a "normal" group. They found that the reflex temperature response of the fingers induced by warming the legs is abnormally slow in lupus erythematosus. In other words, the elapsed time between the

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From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School, Dr. Marion B. Sulzberger, chairman, and the Skin and Cancer Unit of University Hospital.

1. Altschuler, C. H., and Angevine, D. M.: Histochemical Studies on the Pathogenesis of Fibrinoid, Am. J. Path. **25**:1061, 1949.

2. Taylor, H. L., and Huff, S.: Studies of the Peripheral Circulation in Lupus Erythematosus, J. Invest. Dermat. **14**:21, 1950.

immersing of the feet in warm water and the attaining of the highest reflex finger temperature was significantly longer in patients with lupus erythematosus than in "normal" persons. There was also a difference between the two groups in the average finger temperature attained, but the difference was not considered statistically significant.

Taylor and Huff also noted differences in the forms of pulse tracings of patients with lupus erythematosus and of normal persons. The tracings of patients with lupus erythematosus showed a more gradual rise of the ascending limb (i. e., a prolonged crest time), a rounding of the peak of the curve and an obliteration of the dicrotic notch on the descending limb. Similar changes have been noted in arteriosclerosis, hypertension and pseudoxanthoma elasticum and have been ascribed to impaired arterial elasticity. There have been no reports of any attempt at correlation of these observations with the progress, prognosis or response to therapy of lupus erythematosus.

There is also some evidence that there is an alteration of the fluid exchange between the vessels and tissue spaces in lupus erythematosus. Herrmann and I,[3] using the dye fluorescein as an indicator, found areas of increased capillary permeability and fluid exchange in lesions of lupus erythematosus.

Milberg and Carney,[4] using the passive hyperemia test, found that it takes longer to produce erythema and that the erythema takes much longer to clear (normal, 1 and 1.2 minutes; lupus erythematosus, 1.6 and 3 minutes) in persons with lupus erythematosus than in controls. This is attributed to poor elasticity of the vessel walls and/or an imbalance between vasodilator and vasoconstrictor substances.

Attention should also be called to the relation of lupus erythematosus to menstruation as well as pregnancy, its predominance in the female and the place of castration or interruption of pregnancy in therapy. There has always been much speculation on this subject, and at one time lupus erythematosus was considered an indication for the interruption of pregnancy. It is the consensus at present that castration of the female has no place in therapy and that pregnancy should not be interrupted on account of lupus erythematosus.

131 East Seventieth Street (21).

3. Herrmann, F., and Kanof, N. B.: The Fluorescein Pattern of Dermatoses, J. Invest. Dermat. **8**:421, 1947.

4. Milberg, I., and Carney, J.: Personal communication to the author.

# THERAPY OF LUPUS ERYTHEMATOSUS

## Bismuth Sodium Triglycollamate, Sodium Paraaminobenzoate and the Tocopherols (Vitamin E)

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IT IS WELL known that up to the present there has not been a uniformly satisfactory treatment for any type of lupus erythematosus. Because of this and because of ignorance pertaining to the etiology of the disease, enthusiastic reports extolling the beneficial effects of one drug or another frequently have appeared in the literature. In the therapy unit of the Skin and Cancer Clinic my associates and I have attempted to evaluate some of these newer remedies.

*Bismuth Sodium Triglycollamate ("Bistrimate")*[1].—Bismuth is widely employed in the treatment of discoid lupus erythematosus and is generally accepted as a valuable agent in the management of this disease. Each tablet of "bistrimate" contains 410 mg. of bismuth sodium triglycollamate, equivalent to 75 mg. of metallic bismuth. Forty-three patients with discoid lupus erythematosus and 2 persons with subacute disseminated lupus erythematosus were treated with this drug for periods ranging from four to twenty-six weeks. The drug was administered three times daily in doses of 1 tablet after each meal for the first three days and 2 tablets after each meal thereafter.

A gingival bismuth line, mild gastrointestinal upsets and headache were observed with some frequency but were not considered contraindications to continuation of therapy. In 2 patients there developed a stomatitis with trigeminal neuralgia severe enough to warrant cessation of therapy. Four others presented a stomatitis but tolerated reduced doses of the drug. Transient leukopenia was observed in about 20 per cent of the cases, but the blood pictures returned to normal in spite of continuation of treatment.

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From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School, Dr. Marion B. Sulzberger, chairman, and the Skin and Cancer Unit of University Hospital.

1. Pascher, F.; Sawicky, H. H.; Silverberg, M. G., and Emmet, R.: Therapeutic Assays of the New York Skin and Cancer Unit, New York Post Graduate Medical School and Hospital: Assay I—Bistrimate (Bismuth Compound) for Lupus Erythematosus, J. Invest. Dermat. **10**:441-445, 1948.

As a rule, in the cases in which there was a favorable response to administration of bismuth sodium triglycollamate improvement became apparent in approximately four to six weeks after treatment was started. In most cases two to three months were required for the maximum therapeutic effect. Definite improvement in the lesions was noted in 50 per cent of the cases treated, some improvement in 25 per cent and no improvement in 25 per cent. The best response was seen in early cases, that is, those of less than six months' duration. The results in the 2 cases of subacute disseminated lupus erythematosus were not satisfactory.

We are of the opinion that bismuth sodium triglycollamate is at least as effective as bismuth preparations given parenterally in the treatment of chronic discoid lupus erythematosus and is of particular value in the early case.

*Sodium Paraaminobenzoate* [2].—Sodium paraaminobenzoate (specially prepared and supplied by Bristol Laboratories, Inc.) in 0.5 Gm. tablets was administered in doses of 5 tablets (2.5 Gm.) every two hours from 8 a. m. to 12 midnight for a total daily dose of 45 tablets (22.5 Gm.). Thirteen patients with chronic discoid lupus erythematosus were subjected to this regimen for periods ranging from one to five weeks.

Five patients presented a significant reduction in the white blood cells (3,200 to 3,000 white blood cells) with a beginning depression of the granulocytes during the second and third weeks of treatment. One of these had repeated attacks of epistaxis. In all instances the blood pictures returned to normal within two to four weeks after the cessation of therapy. One male patient experienced a widespread dissemination of lesions on the eighth day of treatment. The disseminated lesions cleared within two weeks after cessation of therapy. One woman exhibited a generalized pruritic erythema on the tenth day of treatment. One tablet (0.5 Gm) of the drug, when administered one week later, caused a similar reaction. One woman, during the third week of therapy, found it difficult to carry on with her daily chores because of excessive tiredness and weakness. She refused further treatment or testing with the drug.

Results were rated poor in all 13 subjects, there being no appreciable improvement in the cutaneous manifestations. In 8 cases it was considered advisable to discontinue the drug during the second or third week of therapy because of one or another of the side reactions

2. Rein, C. R., and Sawicky, H. H., in discussion on Zarafonetis, C. J. D.; Grekin, R. H., and Curtis, A. C.: Further Studies on the Treatment of Lupus Erythematosus with Sodium Para-Aminobenzoate, J. Invest. Dermat. **11**:359-381, 1948.

described. We, therefore, could not substantiate the reported [3] benefits of administration of sodium paraaminobenzoate in the treatment of chronic discoid lupus erythematosus. We further concluded that the drug was relatively toxic in the dosage employed in this study.

*Tocopherols (Vitamin E).*—Vitamin E in 200 mg. capsules [4] taken by mouth three times daily was given over a period extending from two to nine months. The average time was three and a half months. In addition, vitamin E in doses of 400 mg.[5] was given intramuscularly twice weekly over the same period. The number of injections received by each of the patients varied between two and sixty; the average number was twenty. A total of 45 patients with chronic discoid lupus erythematosus was placed on this regimen.

With few exceptions, the oral preparations of vitamin E were well tolerated. Repeated blood counts and results of urinalysis failed to reveal any abnormality attributable to the therapy. Six patients exhibited a severe local reaction at the site of the intramuscular injection of vitamin E, accompanied with a transient rise in temperature, chills, nausea and vomiting. Four of these reactions occurred after the first injection, one after the second and one after the third. Subsequent injections were well tolerated. Two patients experienced a recurrence of distress because of an old peptic ulcer while receiving the orally administered vitamin E; 1 could not tolerate the drug because of nausea and vomiting. One patient complained of severe flushing after each injection.

Of the 45 persons treated, 5 showed some improvement and 1 improved but promptly relapsed while receiving this therapy. The results in the remaining 39 cases were considered therapeutic failures.

We failed to substantiate the reported [6] benefits of vitamin E therapy in the treatment of patients with chronic discoid lupus erythematosus.

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3. Zarafonetis, C. J. D.; Grekin, R. H., and Curtis, A. C.: Further Studies on the Treatment of Lupus Erythematosus with Sodium Para-Aminobenzoate, J. Invest. Dermat. **11**:359-381, 1948.

4. E. R. Squibb and Sons supplied the tocopherex® high potency (capsules of distilled mixed natural tocopherols containing 68 mg. of *d*,α-tocopheryl acetate).

5. U. S. Vitamin Corporation supplied the ampuls of 400 mg. of distilled mixed natural tocopherols containing 100 mg. of *d*, α-tocopheryl acetate.

6. Burgess, J. F., and Pritchard, J. E.: Tocopherols (Vitamin E): Treatment of Lupus Erythematosus; Preliminary Report, Arch. Dermat. & Syph. **57**:953-964 (June) 1948.

# TREATMENT OF LUPUS ERYTHEMATOSUS WITH CALCIFEROL, ANTIBIOTICS AND GOLD PREPARATIONS

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EXPERIENCE with calciferol (vitamin $D_2$) in the treatment of lupus erythematosus has been limited to a few therapeutic trials. Charpy,[1] who with Dowling [2] was one of the first proponents of calciferol therapy, found this agent ineffective in lupus erythematosus. Popoff and Ivanov [3] likewise found calciferol of no benefit in 3 cases of lupus erythematosus of the mucous membranes.

There have been surprisingly few publications dealing with penicillin therapy of the disease, although the consensus is that penicillin is of little or no value in the management of either the acute or the chronic form of lupus erythematosus. Franks [4] administered penicillin parenterally in 2 cases of chronic discoid lupus erythematosus. In 1 the eruption remained unchanged, and in the other the disease "became much worse, as shown by the increase in sedimentation rate and the dissemination of the lesions." Kolmer [5] and Strakosch [6] each obtained a good result in a single case of the acute disseminated form, whereas Sweeney [7] reported a therapeutic failure in 1 case.

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This paper is the seventh in a "Symposium on Lupus Erythematosus," held at the Bronx Dermatological Society on Dec. 15, 1949.

From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School, Dr. Marion B. Sulzberger, chairman, and the Skin and Cancer Unit of University Hospital.

1. Charpy, M. J.: Treatment of Cutaneous Tuberculosis with Large Doses of Vitamin $D_2$, Ann. de dermat. et syph. **6**:310-346, 1946.

2. Dowling, G. B., and Prosser, T. E. W.: Treatment of Lupus Vulgaris with Calciferol, Clin. J. **75**:190-184, 1946.

3. Popoff, L., and Ivanov, I.: Lupus Erythematosus of the Mucous Membranes and Its Clinical and Pathogenical Significance, Clin. Bulgara **7**:461-468, 1948.

4. Franks, A. G.; Dobes, W. L., and Romano, D.: Penicillin in the Treatment of Cutaneous Disease, Arch. Dermat. & Syph. **52**:14-16 (July) 1945.

5. Kolmer, L. A.: Penicillin Therapy: Including Streptomycin, Tyrothricin and Other Antibiotic Therapy, ed. 2, New York, D. Appleton-Century Company, Inc., 1947, p. 223.

6. Strakosch, E. A.: Acute Lupus Erythematosus Disseminatus Treated with Penicillin: Report of Case, Arch. Dermat. & Syph. **54**:197-199 (Aug.) 1946.

7. Sweeney, J. S.: Therapeutic Effectiveness of Penicillin in Treatment of Vincent's Stomatitis and Its Failure to Influence Favorably Certain Other Medical Conditions, J. Lab. & Clin. Med. **30**:132-134, 1945.

My associates and I have had no experience with the use of streptomycin, nor have there been any reports in the literature on this antibiotic with the exception of that by Reynaers.[8] He treated 1 patient with chronic lupus erythematosus without benefit. Two of our patients with subacute lupus erythematosus were treated with aureomycin hydrochloride. The medication was administered orally, 1.5 to 3 Gm. daily for a number of weeks, without any apparent change in the lesion or in the course of the disease. This limited experience with streptomycin and aureomycin is neither encouraging nor conclusive.

The first reports on chloramphenicol (chloromycetin®) will appear shortly. Robinson[9] treated 13 patients with chronic discoid lupus erythematosus. For 5 the lesions regressed completely; for 6 there was improvement; for 1 the condition remained unchanged, and for 1 the lesions disseminated during treatment. The results in 3 cases of acute lupus erythematosus disseminatus, on the other hand, were uniformly poor.[10]

Undoubtedly, gold preparations remain one of the best therapeutic agents for chronic discoid and chronic disseminated lupus erythematosus. Many different preparations have been advocated: gold chloride,[11] ammonium succinimidoaurate,[12] gold and sodium thiosulfate,[13] aurothioglucose (solganal®),[14] and, more recently, 2 per cent colloidal gold sulfide combined with nicotinic acid.[15] American dermatologists are still somewhat at variance as to which of these is the most efficacious and the least toxic. This confusion exists because there have been few attempts to evaluate these agents under controlled conditions for comparable cases. It is only through scientifically planned therapeutic assays that one can obtain the answers to these questions.

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8. Reynaers, H.: Un cas de lupus érythémateux traité par streptomycin, Arch. belges dermat. et syph. **5**:50-51, 1949.

9. Robinson, H. M.: Chloramphenicol (Chloromycetin) in the Treatment of Chronic Discoid Lupus Erythematosus, J. Invest. Dermat., to be published.

10. Johnson, S. A. M.; Meyer, O. O.; Brown, J. W., and Rasmusson, A. F., Jr.: Failure of Chloromycetin in Three Cases of Lupus Erythematosus Disseminatus, J. Invest. Dermat., to be published.

11. Haxthausen, H.: Treatment of Lupus Erythematosus by Intravenous Injections of Gold Chloride, Arch. Dermat. & Syph. **22**:77-90 (July) 1930.

12. Obermayer, M. E., and Becker, S. W.: Ammonium Succinimido Aurate: A Gold Compound of Low Toxicity, J. Invest. Dermat. **1**:85-107, 1938.

13. Schamberg, J. F., and Wright, C. S.: The Use of Gold and Sodium Thiosulphate in the Treatment of Lupus Erythematosus, Arch. Dermat. & Syph. **15**:119-137 (Feb.) 1927.

14. Epstein, S., and Jessner, M.: Zur Solganaltherapie von Lupus erythematodes, Tuberkuliden und Acne, Dermat. Ztschr. **73**:1-7, 1936.

15. Schmidt, F. R.: Lupus Erythematosus Treated with Vasodilators and Colloidal Gold Sulfide, Arch. Dermat. & Syph. **56**:248-255 (Aug.) 1947.

Last year we conducted such an assay of colloidal gold sulfide ("aurol" sulfide) combined with nicotinic acid as recommended by Schmidt.[16] Forty-six patients with chronic discoid lupus erythematosus were treated, and the results were as follows:

| | |
|---|---|
| Healed | 9, or 19% |
| Striking improvement | 15, or 34% |
| Moderate improvement | 11, or 23% |
| Some improvement | 3, or 6% |
| Unimproved | 8, or 17% |
| Relapse | 0 |

In comparing these figures with those of our previous therapeutic assay with oral bismuth therapy (bismuth sodium triglycollamate ["bistrimate"]) [17] we were able to show that the results with this oral bismuth therapy compared favorably with colloidal gold sulfide combined with nicotinic acid.

| | Colloidal Gold Sulfide and Nicotinic Acid Patients Treated: 46 | Bismuth Sodium Triglycollamate Patients Treated: 45 |
|---|---|---|
| Healed | 9, or 19% | 5, or 11% |
| Improved | 29, or 63% | 30, or 67% |
| Unimproved | 8, or 17% | 8, or 17% |
| Relapse | 0 | 2, or 4% |

Statistics on the toxic effects of this form of gold therapy also were made available. Hematologic manifestations of toxicity occurred in 40 per cent and renal manifestations in 9 per cent of the patients treated. A depression in the leukocyte count was the outstanding untoward effect. The administration of colloidal gold sulfide, as well as the administration of any other gold preparation, should be controlled by repeated leukocyte counts and urinalyses. Weiss and his co-workers [18] emphasized the importance of the leukocyte count as a guide to dosage. We have found that, even in the presence of mild leukopenia or albuminuria, with smaller doses and with interspersed rest periods therapy could be continued without apparent progressive damage.

16. Pascher, F.: Silverberg, M. G.; Loewenstein, L. W., and Sawicky, H. H.: Therapeutic Assays of New York Skin and Cancer Unit, Post Graduate Medical School, New York University—Bellevue Medical Center: Assay III—Aurol-Sulfide (Hille), J. Invest. Dermat. **13**:151-155, 1949.

17. Pascher, F.; Sawicky, H. H.; Silverberg, M. G., and Emmet, R.: Therapeutic Assays of New York Skin and Cancer Unit, New York Post Graduate Medical School and Hospital: Assay I—Bistrimate for Lupus Erythematosus, Lichen Planus and Other Dermatoses, J. Invest. Dermat. **10**:441-445, 1948.

18. Weiss, R. S.; Lane, C. W., and Bagby, J. W.: Effect on the Leukocytes of Therapy with a Gold Preparation, Arch. Dermat. & Syph. **35**:1074-1086 (June) 1937.

In 1936, Wright [19] reported on his experience with gold compounds in the treatment of lupus erythematosus. The majority of his patients were treated with gold and sodium thiosulfate. I should like to compare the results obtained with gold and sodium thiosulfate with those obtained with 2 per cent colloidal gold sulfide combined with nicotinic acid.

| | Colloidal Gold Sulfide and Nicotinic Acid Patients Treated: 46 | Gold and Sodium Thiosulfate Patients Treated: 76 |
|---|---|---|
| Healed | 9, or 19% | 28, or 37% |
| Greatly improved | 15, or 34% | 26, or 34% |
| Improved | 14, or 30% | 13, or 17% |
| Unimproved | 8, or 17% | 9, or 12% |
| Untoward reaction* | 22, or 49% | 19, or 24% |

* Blood counts were not done, which fact probably accounts for the striking difference in the percentage of untoward reactions.

The results with gold and sodium thiosulfate appear to be at least as good as those with colloidal gold sulfide. We did not follow the patients treated with colloidal gold sulfide long enough to permit any conclusions as to the percentage of relapses. Wright [19] reported that 13 of 76, or 17 per cent, suffered one or more relapses, and Callaway and Stokes [20] reported 22 of 31, or 74 per cent, had anywhere from one to four relapses subsequent to cessation of therapy. These relapses occurred without relation to time, sex, race, total or average dose of gold and sodium thiosulfate.

In conclusion, I may say that gold preparations used with the background of dermatologic knowledge and with care constitute probably the best therapeutic agent we have today for the chronic forms of lupus erythematosus, but much remains to be desired. The therapeutic failures, the relapses and the many possible untoward effects compel us to search for a better form of therapy.

80 Linden Boulevard.

19. Wright, C. S.: Ten Years' Experience in the Treatment of Lupus Erythematosus with Gold Compounds, Arch. Dermat. & Syph. **33**:413-433, 1936.

20. Callaway, J. L., and Stokes, J. H.: Relapse in Lupus Erythematosus After Treatment with Sodium Gold Thiosulphate, Arch. Dermat. & Syph. **37**:627-630 (April) 1938.

# EFFECT OF PITUITARY ADRENOCORTICOTROPIC HORMONE (ACTH) ON DISSEMINATED LUPUS ERYTHEMATOSUS

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CHARLES RAGAN, M.D.
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SINCE Hench and his co-workers [1] described the dramatic effect of cortisone and pituitary adrenocorticotropic hormone, or ACTH, on patients with rheumatoid arthritis, interest in the effect of these substances on the "mesenchymal diseases" has mounted. Independent reports by Boland and Headley in Los Angeles,[2] Thorn in Boston [3] and Ragan and co-workers in New York [4] amply confirmed that there are beneficial effects observed in rheumatoid patients. Only scattered reports

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Supported in part by grants from the Masonic Foundation for Medical Research and Human Welfare and the Office of Naval Research, United States Navy.

From the Departments of Medicine, Surgery and Surgical Pathology, Columbia University College of Physicians and Surgeons, and the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital.

1. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: The Effect of a Hormone of the Adrenal Cortex (17-Hydroxy-11-Dehydrocorticosterone: Compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis: Preliminary Report, Proc. Staff. Meet., Mayo Clin. **24**:181, 1949.

2. Boland, E. W., and Headley, N. E.: Effects of Cortisone Acetate on Rheumatoid Arthritis, J. A. M. A. **141**:301 (Oct. 1) 1949.

3. Thorn, G. W.; Bayles, T. B.; Wassell, B. F.; Forsham, P. H.; Hill, S. R.; Smith, S., and Warren, J. E.: Studies on the Relation of Pituitary-Adrenal Function to Rheumatic Disease, New England J. Med. **241**:529, 1949.

4. Ragan, C.; Grokoest, A. W., and Boots, R. H.: Effect of Adrenocorticotrophic Hormone (ACTH) on Rheumatoid Arthritis, Am. J. Med. **7**:741, 1949

from Hench,[1] Thorn,[3] Grace [5] and others [6] to the time of writing indicated beneficial results from this therapy in other members of the group of connective tissue disorders which includes rheumatic fever, scleroderma, dermatomyositis, periarteritis nodosa and disseminated lupus erythematosus.

This report deals with 3 patients with disseminated lupus, erythematosus, observed on the medical service of the Presbyterian Hospital, who were treated with ACTH. Experimental work conducted in an effort to explain the effect of the adrenal hormones on this disease is presented in another paper.

## REPORT OF CASES

CASE 1.—A. B. was a 23 year old Negro woman whose illness had begun about one and a half years previous to the time of writing with widespread joint involvement suggestive of rheumatoid arthritis. She was admitted to the hospital for the first time on May 27, 1949, because of a week of temperatures ranging to 104 F. Pertinent observations were tender swollen joints, tachycardia, left pleural and pericardial effusions, anemia, leukopenia, albuminuria with occasional microscopic hematuria, serum globulin of 5.3 Gm. per hundred cubic centimeters and a cephalin flocculation reaction of 4 plus. She responded symptomatically to administration of acetylsalicylic acid and thoracenteses. She was investigated neurologically because of headaches and forgetfulness. Cerebrospinal fluid protein was slightly elevated, and there were electroencephalographic abnormalities. The patient was discharged on July 2, 1949, on treatment with acetylsalicylic acid, but promptly had a severe relapse and was readmitted three weeks later. At that time her temperature was 104.4 F. and in addition to the previously noted observations she had a spotty erythematous rash and 2 plus papilledema. Pertinent observations during her course are presented in figure 1. Before ACTH was administered, there was a high fever and the patient experienced one grand mal seizure. Increased cerebrospinal fluid pressure was relieved by frequent lumbar punctures. On August 30 treatment was begun with ACTH in doses of 60 to 80 mg. a day, and this was continued until September 28. There was an immediate dramatic drop in temperature which persisted while the patient was on treatment with ACTH. Thoracenteses were no longer necessary. After a temporary rise, the sedimentation rate came down. Headache and joint pains responded promptly. Cephalin flocculation and thymol turbidity reactions reverted to negative. There was a striking gain in weight which was largely due to accumulation of interstitial fluid and disappeared promptly on discontinuance of ACTH therapy. Shortly after the treatment with ACTH was started this patient acquired a moderately severe parotitis which failed to respond to chemotherapy. Incision and drainage was performed, and it was noted that

5. Grace, A. W., and Combes, F. C.: Remission of Disseminated Lupus Erythematosus Induced by Adrenocorticotropin, Proc. Soc. Exper. Biol. & Med. **72**:563, 1949.

6. Ragan, C.: The Effect of ACTH on the Clinical Syndrome of Dermatomyositis, in Mote, J. R.: Proceedings of the First Clinical ACTH Conference, New York, The Blakiston Company, 1950. Bassett, S. H., and White, A.: The Effect of ACTH on One Case of Periarteritis Nodosa, ibid. Bayles, T. B., and Stillman, J. S.: The Effect of ACTH on Scleroderma, ibid. Howard J. E.: Preliminary Report on the Results of ACTH in the Hypersensitive States, ibid.

no granulation tissue formed at the site of the parotid abscess for twenty days while ACTH was given. Within four days of discontinuance of treatment with the drug granulation tissue formed, and the wound subsequently healed.[7] Other significant observations noted during treatment included typical Cushing's facies and purplish abdominal striae. Two days after the use of ACTH was discontinued, the patient's temperature reached 104 F. and she manifested a severe paranoid

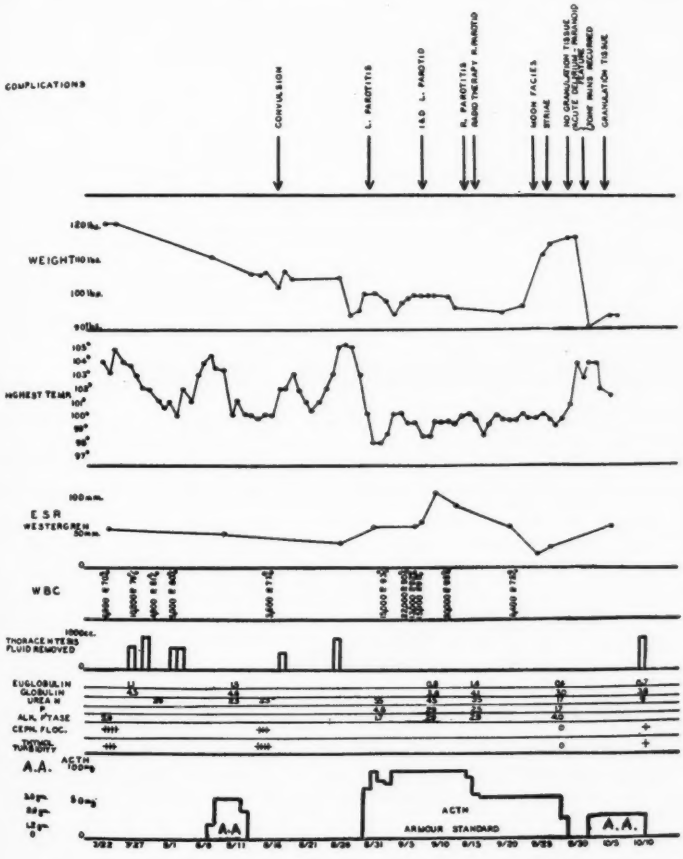


Fig. 1.—Observations made during the course of the disease for A. B. (case 1). *A.A.* indicates acetylsalicylic acid.

psychosis which necessitated her transfer to the Psychiatric Service of Bellevue Hospital, where she was at the time of writing. Her disseminated lupus returned to its pretreatment level. It is probable that this patient had an organic psychosis unrelated to treatment with ACTH.

7. Calder, K. T.: Personal communication to the authors.

Case 2.—L. H., a 37 year old Negro woman had been ill for over a year with fever, arthritis, pleurisy, purpura, albuminuria and microscopic hematuria, mild hyperglobulinemia, a positive cephalin flocculation reaction and relative leukopenia with no response to treatment with acetylsalicylic acid, aureomycin and penicillin. She had had a splenectomy in 1947 for what was thought to be thrombopenic purpura. She was given ACTH in varying doses, averaging 60 mg., with prompt remission of her arthritis and fever and a great increase in her sense of well-being. However, while under treatment she acquired hypertension (fig. 2), which was probably due to the presence of posterior pituitary extract. Her blood pressure rose from 100 systolic and 60 diastolic to 180 systolic and 110 diastolic,

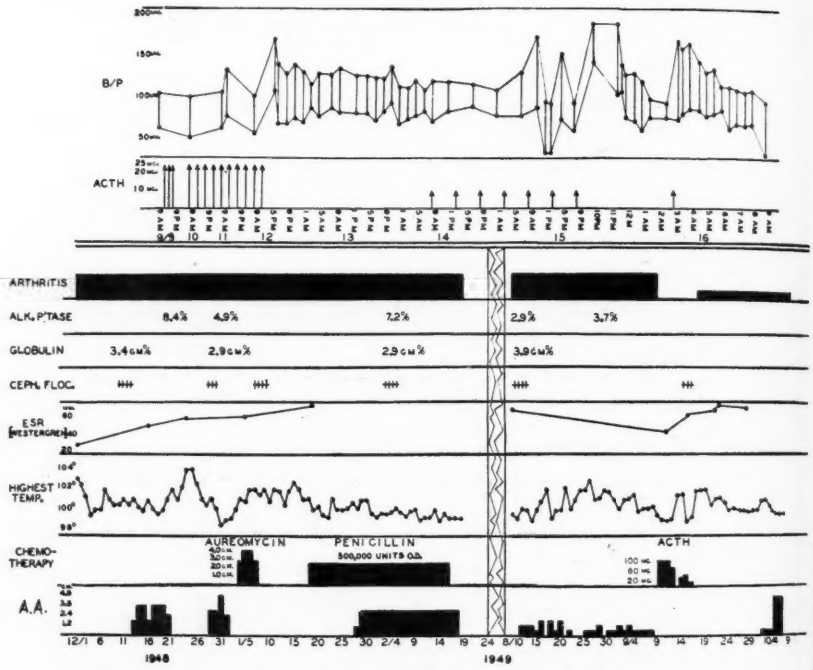


Fig. 2.—Observations made during the course of the disease for L. H. (case 2). *A.A.* indicates acetylsalicylic acid.

and on the sixth day of treatment she had a severe occipital headache which was shown to be due to subarachnoid hemorrhage. Administration of ACTH was discontinued and symptoms returned, but to a more moderate degree, for several days. She made a fairly good recovery from her subarachnoid hemorrhage and was discharged on treatment with acetylsalicylic acid. She returned to the hospital one month later with pneumococcal pneumonia and meningitis which responded to therapy, but at the time of writing she was still critically ill and evidence of lupus was still present.

Case 3.—P. S., a 23 year old graduate nurse, had been followed since 1946 when, as a student nurse, she had noticed a rash over her eyes and forehead which

was believed to be due to sensitivity to adhesive plaster. In 1947 she acquired a disease characterized by arthritis, lymphadenopathy, splenic enlargement, a positive cephalin flocculation reaction, fever and pronounced asthenia. She was thought to have atypical infectious mononucleosis and was seen frequently over the course of the next year and half because of recurrent arthritis, asthenia, mild fever, elevation of sedimentation rate and a persistently positive cephalin flocculation reaction. In 1948 her condition had improved somewhat and she was married. She became pregnant but felt ill toward the end of her pregnancy. After delivery, during the course of which she had an episiotomy, she manifested high fever, delirium and pronounced signs of toxicity. Her arthritis became severe, and

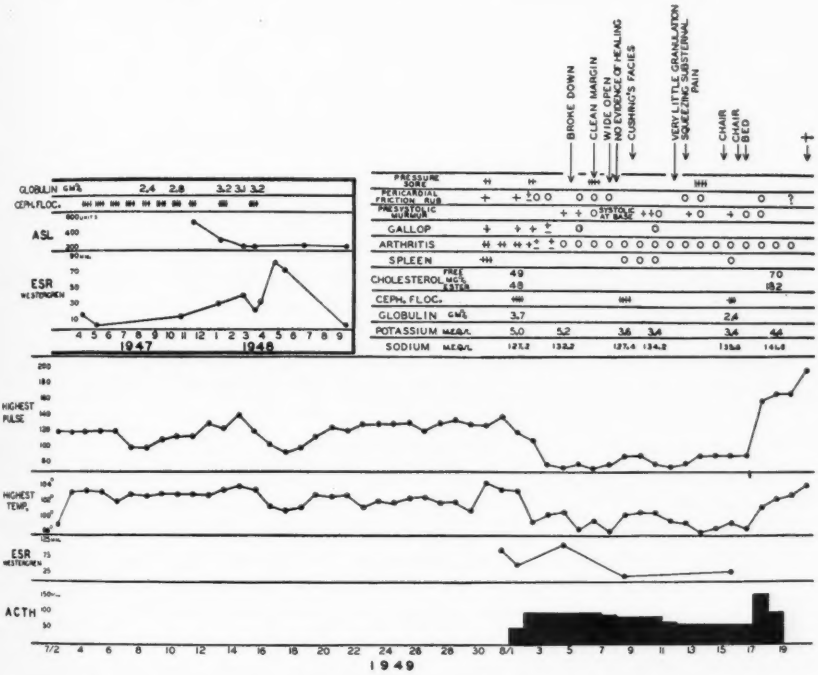


Fig. 3.—Observations made during the course of the disease for P. S. (case 3). *ASL* indicates the antistreptolysin titer.

cardiac gallop rhythm was noted. She was transferred from Maine to the Presbyterian Hospital, where her course was that of a critically ill patient. Before treatment with ACTH was instituted, she had persistent fever, intermittent delirium, pericardial friction rub, gallop rhythm and splenomegaly and she acquired a decubitus ulcer. On August 1 she began to be treated with a course of ACTH, with doses varying on an average from 60 to 100 mg. daily. There was prompt disappearance of arthritis and pericardial friction rub, and the temperature and pulse rate declined almost to normal levels. The spleen could no longer be felt, and the patient subjectively was improved although her condition continued critical. Her episiotomy wound healed poorly over the course of her illness,

and while ACTH was administered, despite the favorable effects otherwise, further granulation tissue failed to develop. The decubitus ulcer, despite intensive treatment, also remained wide open with no evidence of healing. The patient acquired "squirrel facies" but no hypertension. After sixteen days of treatment she was allowed out of bed; afterward she had pain in the chest, dyspnea, fever and tachycardia despite continuous ACTH therapy, and shortly thereafter she died because of what was thought clinically to be a pulmonary infarction. Dr. Klemperer reviewed the pathologic sections and confirmed the impression of disseminated lupus erythematosus. Grossly, the adrenal glands weighed together 45 Gm., which is about three times normal. This hypertrophy was shown microscopically to be due largely to enlargement and vacuolization of the cells of the adrenal cortex. The lungs showed acute hemorrhagic pulmonary infarction which was the immediate cause of death. There were thrombi in the perivesical venous plexus. The heart grossly showed thickening of the mitral valve and about the foramen ovale with verrucae—the so-called Libman-Sacks disease. There was acute fibrinous pericarditis with effusion. Retroperitoneal lymph nodes showed collections of cells which have been described as characteristic of disseminated lupus erythematosus. Sections of the episiotomy wound and decubitus ulcer showed no fresh granulation tissue.

As can be seen from these cases, ACTH exerts a definite effect on the course of disseminated lupus erythematosus. The ultimate outcome in all 3 cases was unfavorable, but it is unfavorable in this disease in general. In all patients such favorable effects occurred as prompt disappearance of fever and pain, decrease in inflammatory reaction of serous surfaces, return to normal of abnormal laboratory observations such as hyperglobulinemia and elevated sedimentation rate and cephalin flocculation and a general improvement in well-being. No therapeutic agents other than ACTH and cortisone have been shown to have this effect. In the 2 patients who survived, however, all the beneficial effects disappeared promptly on withdrawal of the drug. Some danger is inherent in treatment with ACTH, as is exemplified by the complications which occurred while the patients were under treatment. In 1 patient hypertension and subarachnoid hemorrhage presented a threat to life and necessitated discontinuance of therapy. This condition may have been due to the presence of posterior pituitary extract, of which more recent preparations of ACTH have contained less. In another patient there was precipitous gain in weight and prevention of healing of an open wound. The patient who died of pulmonary infarction, despite her early favorable response, showed failure of healing of two open wounds.

To summarize this limited experience, then, ACTH exerted a powerful but temporary beneficial effect on the course of 3 cases of disseminated lupus erythematosus, but at the present state of knowledge this preparation must be used with great caution. It seems possible that further investigation with this compound and possibly other steroids may result in a safer method of treatment to cause remission of or favorably affect this otherwise fatal disease.

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# ACTION OF CORTISONE ON MESENCHYMAL TISSUES

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OF FUNDAMENTAL importance is knowledge of the mechanism of action of those adrenal hormones which act beneficially in disseminated lupus erythematosus and other diseases of tissues of mesenchymal origin. Two of the patients described in our clinical discussion [1] showed failure to form granulation tissue while being treated, and 1 had prompt healing when treatment with pituitary adrenocorticotropic hormone (ACTH) was discontinued. In other patients, with rheumatoid arthritis, similar observations have been made.[2] The question arose of whether ACTH and cortisone might not act by altering the host response to the disease, that is, by halting a connective tissue process which results in the various clinical entities of these diseases.

Accordingly, an experimental evaluation of the effect of various steroids on the connective tissues is going on in our laboratories. Pre-

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From the Departments of Medicine, Surgery and Surgical Pathology, Columbia University College of Physicians and Surgeons, and the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital.

Supplies of cortisone were obtained from Merck & Co., Inc., through the Committee on Cortisone Research of the National Academy of Sciences, purchased by funds from the United States Public Health Service.

Supported in part by grants from the Masonic Foundation for Medical Research and Human Welfare, the Medical Research and Development Board, Office of the Surgeon General, United States Army, and Office of Naval Research, United States Navy.

1. Plotz, C. M.; Blunt, J. W., and Ragan, C.: Effect of Pituitary Adrenocorticotropic Hormone (ACTH) on Disseminated Lupus Erythematosus, Arch. Dermat. & Syph., this issue, p. 913.

2. Ragan, C.; Grokoest, A. W., and Boots, R. H.: Effect of Adrenocorticotrophic Hormone (ACTH) on Rheumatoid Arthritis, Am. J. Med. **7**:741, 1949.

liminary data [3] indicate that cortisone administered to rabbits exerts a profoundly inhibitory effect on the development of granulation tissue. Skin wounds were made on the ears of several pairs of rabbits. One rabbit of each pair was pretreated for three days with cortisone acetate, and treatment was continued until the animal was killed. The other animal of each pair received identical treatment except that no cortisone was administered. Rabbits were killed five and eight days postoperatively. Photomicrographs of the wounds are shown in figure 1.

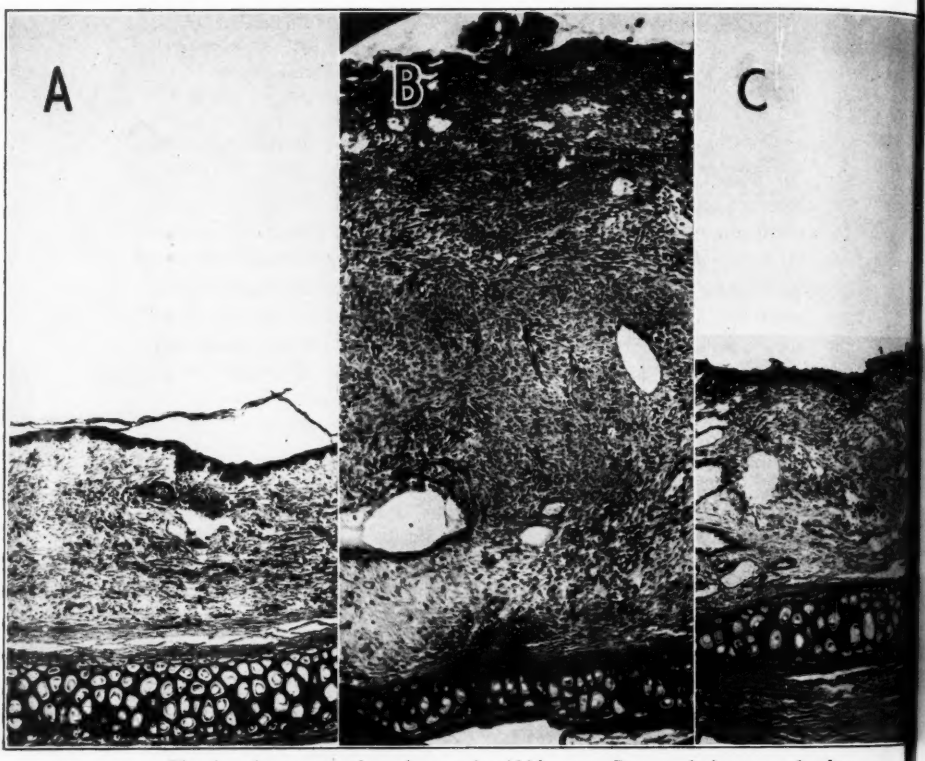


Fig. 1.—*A*, cross section of normal rabbit's ear. *B*, granulating wound, after eight days, in control rabbit. *C*, granulating wound, after eight days, in animal treated with cortisone.

Figure 1 *A* shows a cross section of a normal rabbit's ear. Figure 1 *B* shows a cross section through the ear wound on the eighth postoperative day. The cartilage is on the bottom, and one can note the great thickness

3. Ragan, C.; Howes, E. L.; Plotz, C. M.; Meyer, K., and Blunt, J. W.: Effect of Cortisone on Production of Granulation Tissue in the Rabbit, Proc. Soc. Exper. Biol & Med. **72**:718, 1949.

of the granulation tissue with much ground substance, vigorous fibroplasia and the appearance of many new blood vessels. Contrast this picture with that seen for the section taken from the cortisone-treated rabbit (fig. 1 *C*), killed also on the eighth postoperative day. In it the zone of granulation tissue is decidedly narrowed. Fibroblasts are closely packed about old blood vessels, and few, if any, new blood vessels are seen.

The suppressive effect of cortisone on the connective tissues suggests that its effect in the human being is one of depression of activity of these tissues, resulting in remission of symptoms. Host reactivity alone is affected, and the precipitating or maintaining trauma is not disturbed. Thus, when administration of the drug is discontinued, the connective tissues again react and relapse occurs. In figure 2 this concept is pre-

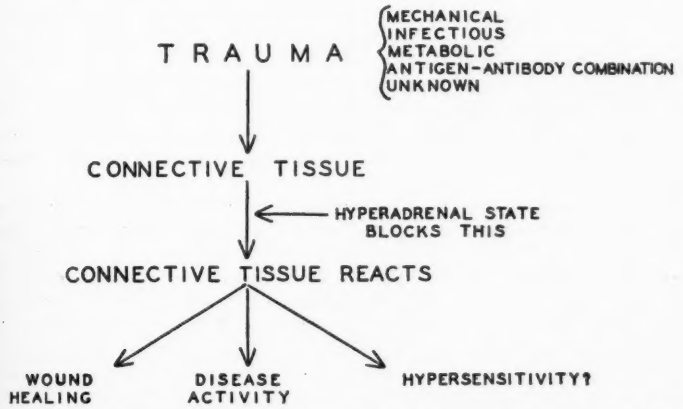


Fig. 2.—Schematic presentation of concept of the action of cortisone and ACTH.

sented schematically. This schema may help to explain the basis for the beneficial action of cortisone in diseases with a wide variety of clinical manifestations and probably with as wide a variety of etiologic agents.

## SUMMARY

1. The mechanism of action of cortisone on mesenchymal diseases is being investigated by an experimental wound technic.

2. Cortisone administered to rabbits in large enough doses to produce a hyperadrenal effect resulted in a striking depression of activity of connective tissue.

3. It is suggested that the beneficial action of cortisone and ACTH in the "mesenchymal diseases" may be related to this depressive effect on host reactivity.

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## ABSTRACT OF DISCUSSION

### On Papers in the Symposium on Lupus Erythematosus

Dr. Marion B. Sulzberger, New York: The presentation by Dr. Haserick deals with one of the highlights of experimental work in dermatology in this country, and perhaps the world, in recent years. To my mind, Haserick's and Hargraves' work with the L. E. cell ranks, with some of the other recent investigations, such as Nelson's on the antibody inactivating Treponema pallidum, among the most significant recent contributions and the greatest steps in medical progress. What particular item or facet I should discuss is a problem. To select one aspect quite arbitrarily: the observations concerning the L. E. cell suggest that there may be no identity of cause in such syndromes or pictures as acute disseminated lupus erythematosus and chronic discoid lupus erythematosus and that lupus erythematosus of either type is probably not identical with dermatomyositis, scleroderma and other conditions which, after they had been separated from one another by many years of painstaking investigations by keenly observant dermatologists were in real danger of being lumped together again under such terms as the "collagen disease."

If the L. E. cell is a pathognomonic feature of acute disseminated lupus erythematosus, as it now appears to be, then the absence of this cell in other diseases is at least highly suggestive that the fundamental processes in these other diseases must differ in essential respects from those of acute disseminated lupus erythematosus.

In Dr. Gueft's excellent work with Klemperer a great forward step is certainly being made by means of the attempt to identify the actual chemical nature of the nuclear material in the altered polymorphonuclear leukocytes or L. E. cells demonstrated by Dr. Haserick. The advance may be slow and groping, but nevertheless there is an approach to more exact knowledge of the nature of acute disseminated lupus erythematosus, and in the results there may be the first real clues to the causes of the disease. For example, if the material in the L. E. cell is desoxyribosenucleic acid, then perhaps there is some relation between the present observations in the L. E. cell and those recently reported by Geoffrey Rake of E. R. Squibb and Sons and Harvey Blank of Philadelphia regarding the alteration and liberation of nuclear material under the influence of herpes simplex virus.

Time precludes the discussion of the excellent reports by Drs. Kostant, Kanof, Sawicky and Pascher, who, with me, are members of the same institution. I shall have many opportunities to talk over the substance of their presentation.

I would, however, like to say that it was refreshing to hear the presentation of Dr. Plotz, of the College of Physicians and Surgeons. I hope that Dr. Plotz will agree with me that in the present state of knowledge it is not always a favor to the patient to give him cortisone or ACTH. The reasons are the not always avoidable serious side effects and also the present practical impossibility of maintaining patients on sufficiently prolonged schedules of these remedies to keep their disease under permanent control. Moreover, it appears to me quite certain that these materials do not cure most of the diseases they so strikingly benefit. Apparently they influence some basic components in the complex forming the reaction patterns of the host. Thus they alter in one direction or another the reactions of the patient's adaptation mechanisms, including either the specific acquired alterations in capacity to react or the primary reaction capacity of the tissues being attacked, or both. The effects can thus include a great variety of toxic and allergic mechanisms of disease.

A short time ago, at a conference held by Dr. Mote, Dr. Currier McEwen and Dr. Joseph Bunim, I heard Dr. Mote state the opinion that these agents might also have a profound effect on the epithelial and epidermal diseases. One more conclusion to be made regarding the work of Dr. Plotz and others is that the fact that such different pictures or different syndromes as arthritis, asthma, gout, psoriasis and acute disseminated lupus erythematosus often respond in such miraculous fashion to administration of these agents should not and must not be regarded as proof that there is any causal relation between these different conditions. Moreover, the very fact that such therapy is decidedly effective in such widely different diseases is pretty good evidence that with it one is not striking at the causes of these diseases but is knocking out either one common link or perhaps several common links in the chain of their pathogenetic mechanisms.

Dr. Richard S. Weiss, St. Louis: It has been a pleasure for me to be here and listen to this symposium. My associates and I also have been studying the L. E. cell, having started about six months ago. We have confirmed everything that Dr. Haserick has done, with one exception, and everything that Dr. Hargraves has done. We repeated their work and searched for the L. E. cell, trying to demonstrate the L. E. phenomenon in numerous control cases, including cases of subacute disseminated lupus erythematosus, discoid lupus erythematosus, scleroderma and rheumatoid arthritis, and in no disease, except acute disseminated lupus erythematosus, were we able to demonstrate the L. E. phenomenon. There was only one other disease in which Hargraves was able to demonstrate this phenomenon, namely, multiple myeloma, in an isolated case.

We have been able to induce this phenomenon by a simpler method, making it almost an office procedure. The buffy coat, from normal blood is added to serum from a patient with acute lupus erythematosus. Within thirty minutes we are able to produce on a glass slide the L. E. phenomenon: the clumping of the white cells, the formation of rosettes and finally the typical L. E. cell. One does not have to employ either human sternal marrow or marrow from dogs. The only work of Haserick's we have not as yet been able to confirm is the finding of the L. E. factor in the gamma globulin fraction in cases of acute lupus erythematosus.

Dr. Aldo Castellani, Lisbon, Portugal: We have been listening to some wonderful communications. As an investigator of tropical disease, I have always been interested in lupus erythematosus. This disease, both the discoid and the generalized types, is much commoner in the tropics than most people believe. The information on the investigations described will be extremely useful both to the patient and to the practitioner.

I would say a word on an extremely simple treatment of discoid lupus erythematosus in the incipient stage. I am almost ashamed to describe this simple treatment after hearing so much about the newer scientific methods. It is the so-called quinine–salicylic acid treatment. Quinine dihydrochloride is given by mouth in doses of 5 grains (0.30 Gm.); locally a lotion of 2 Gm. of salicylic acid in 100 Gm. of pure alcohol is applied three times daily, and afterward an ointment containing 1 per cent salicylic acid is applied. This treatment has given good results in the tropics.

Dr. Samuel M. Peck, New York: These presentations overwhelm me. It was only yesterday that we knew nothing of the mechanism involved in the causation of lupus erythematosus, either the acute or the discoid type. As a matter of fact, we often considered these types just phases of the same disease. When I think of the innumerable arguments between the internists and the dermatologists

at the Mount Sinai Hospital concerning differential diagnosis in conditions resembling acute lupus erythematosus, I can only be grateful for the material that has just been presented.

It is now many years since I attempted by means of the moccasin venom test to differentiate acute lupus erythematosus from conditions which resembled it. I noted that intradermal injection of titrated moccasin venom gave positive reactions in some cases of acute lupus erythematosus but that the reactions were never positive in erythema multiforme, drug eruptions or discoid lupus erythematosus. The test did not give positive reactions in those cases in which the patients eventually did well but which could be classified at the time of the test as acute lupus erythematosus. My concept of the results of the test was that all that were being measured were degrees of capillary fragility induced by varying concentrations of toxic substances circulated in the blood. I note from the current presentation that it is not uncommon to find capillary fragility in acute lupus erythematosus, as evidenced by the subarachnoid hemorrhage following a rise in blood pressure after treatment with cortisone.

I think that the remarks of Dr. Sulzberger concerning the possible mechanism of the improvement following the use of cortisone are significant. He pointed out that the cortisone might be interfering with reactions instead of affecting a basic etiologic factor. Such a contention is borne out by our past experiences with various pharmacologic agents in the treatment of lupus erythematosus. The reason a number of pharmacologically different substances were able to influence this condition in some instances was also that they interfered with some phases of the pathologic reaction.

The demonstration of the L. E. cell or the failure to demonstrate it or the failure to demonstrate the specific immunologic factors in the blood serum which are responsible for the L. E. cell has influenced me profoundly in my treatment of the condition. I have not hesitated to use agents such as neoarsphenamine (neosalvarsan®) or suramin (naphuride®) in those cases in which either the L. E. cell or the specific immunologic factors were lacking. Fortunately, the use of these agents was not accompanied by any toxic sequelae. I have always felt that the use of the substances previously mentioned was contraindicated in true acute lupus erythematosus because of the possibility of kidney damage and possible cardiovascular accidents.

Dr. Herman Beerman, Philadelphia: I shall limit myself to remarks on the papers by the group from the Skin and Cancer Unit. Since so many false positive serologic reactions have been associated with lupus erythematosus, one would be naive to think that bismuth preparations work in lupus erythematosus because of associated syphilis. It also seems to me that it is rather difficult to determine whether the positive reactions are true or false. Has Nelson's technic been applied to the blood of patients with lupus erythematosus?

Many treatments have been used in lupus erythematosus. In many cases in which the lesion is minimal and causing the patient no particular harm except disfigurement, treatment may be rather disturbing. One might almost be tempted to think that the treatment might cause more trouble in these patients than would the disease.

# PITYRIASIS RUBRA PILARIS: A CLINICAL STUDY

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DESPITE the fact that pityriasis rubra pilaris was first described almost a hundred years ago,[1] there are still many gaps in knowledge of the clinical course, extracutaneous manifestations and pathogenesis of the disease. Our interest was recently drawn to this subject when we saw, within a relatively short time, 2 patients in whom a diagnosis of pityriasis rubra pilaris had been made, both of whom presented clinical evidence of concomitant neuromuscular disease. We felt, therefore, that a review of a larger group of cases of pityriasis rubra pilaris might shed further light on this interesting observation. This report represents a clinical analysis of 58 cases in which a diagnosis of pityriasis rubra pilaris was made at the Mayo Clinic.

The first reported treatment of this disease with vitamins was that of Pettler,[2] who had 2 patients, both of whom had been on vitamin-deficient diets for years. Their lesions gradually disappeared in four and eight months, respectively, after they were given vitamin capsules containing unspecified amounts of vitamins A, B and D.

In 1941, Brunsting and Sheard [3] studied 3 patients who had pityriasis rubra pilaris, in all of whom the threshold of adaptation to the dark was elevated. Repeated tests showed normal results within two to four weeks after a daily dose of 150,000 international units of vitamin A had been started, while, at the same time, the cutaneous eruption showed evidence of clinical improvement.

In nearly all cases of pityriasis rubra pilaris in which laboratory investigations have been carried out, either the blood level of vitamin A or the threshold of dark adaptation or both were abnormal prior to

* From the Section on Dermatology and Syphilology, Mayo Clinic.

1. Devergie, A., cited by Leitner and Ford: Brit. J. Dermat. **59**:407-427 (Dec.) 1947.

2. Pettler, M. F.: Pityriasis Rubra Pilaris, with Particular Reference to Vitamin Medication and Dietary Control, Pennsylvania M. J. **39**:864-866 (Aug.) 1936.

3. Brunsting, L. A., and Sheard, C.: Dark Adaptation in Pityriasis Rubra Pilaris, Arch. Dermat. & Syph. **43**:42-59 (Jan.) 1941.

treatment with vitamin A.[4] Thus it can be seen that the relation between deficient utilization of vitamin A and pityriasis rubra pilaris has been well established. It must be remembered, however, as Porter and Godding [5] pointed out, that usually only diminished intake is considered; absorption, storage, circulation levels, conversion of carotene to vitamin A, synthesis of vitamin-protein compounds required by different tissues and the ability of the tissues themselves to utilize these compounds may be of equal importance and significance.

Mellanby [6] reported, in 1931, that in dogs fed a diet rich in cereals and deficient in vitamin A there occurred a condition resembling subacute combined degeneration of the spinal cord in man, with demyelination of the nerve fibers. He further observed degenerative changes in the trigeminal nerve of dogs receiving a diet deficient in vitamin A, and he suggested that the xerophthalmia associated with clinical deficiency of vitamin A might be due to degeneration of the nerves of the cornea. In view of this experimental evidence and our experience with the 2 aforementioned patients with neuromuscular dysfunction, we sought to determine clinically whether such an association existed.

## QUESTIONNAIRE AND REPLIES

In order to get information concerning the clinical course of the disease so that we might corroborate or disprove this thesis, we sent questionnaires to each of the 58 patients in this group. Thirty-one replies were received. The questions and a summary and analysis of the replies follow:

QUESTION 1.—*How does the condition of your skin compare with what it was at the time of your last visit to the clinic?*

The ultimate prognosis of patients with pityriasis rubra pilaris is apparently not well established, inasmuch as only general and broad references to this aspect of the disease are made in the literature and standard textbooks of dermatology. Ormsby and Montgomery [7] stated that the prognosis is unfavorable with respect to the cutaneous manifestations, as in those cases in which the disorder disappears temporarily it almost invariably recurs; the tendency of the disease is to

4. Leitner, Z. A., and Ford, E. B.: Vitamin A and Pityriasis Rubra Pilaris, Brit. J. Dermat. **59**:407-427 (Dec.) 1947.

5. Porter, A. D., and Godding, E. W.: Pityriasis Rubra Pilaris and Vitamin A, Brit. J. Dermat. **57**:197-200 (Nov.-Dec.) 1945.

6. Mellanby, E.: The Experimental Production and Prevention of Degeneration in the Spinal Cord, Brain **54**:247-290 (Sept.) 1931.

7. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 7, Philadelphia, Lea & Febiger, 1948, p. 344.

persist indefinitely. Andrews [8] observed that the disease may be slowly or rapidly progressive for years, with periods in which it may remain stationary for a time, or that it may regress, eventually disappearing entirely.

A complete tabulation of replies to this question is seen in table 1. As would be expected, the greatest number of reports were received from patients for whom the follow-up period was one to five years. All but 4 of all the patients replying stated that they had improvement in, or complete absence of, their cutaneous lesions. With full awareness of the statistical errors inherent in so small a study group as this, we nevertheless find it interesting to hypothesize that perhaps the prognosis (with regard to the cutaneous manifestations of the disease) is not too dismal.

TABLE 1.—*Follow-Up Data in Thirty-One Cases of Pityriasis Rubra Pilaris*

| Follow-Up Period, Years | Total No. of Cases | Condition | | | |
|---|---|---|---|---|---|
| | | Free of Lesions | Improved | Same | Worse |
| 1-5 | 17 | 8 | 7 | 1 | 1 |
| 6-10 | 7 | 3 | 4 | .. | .. |
| 11-15 | 3 | 1 | 1 | 1 | .. |
| 16-20 | 3 | 1 | 2 | .. | .. |
| 21-25 | 1 | .. | .. | 1 | .. |
| Total | 31 | 13 | 14 | 3 | 1 |

TABLE 2.—*Best Treatment, in Patients' Opinions*

| Best Treatment | No. of Patients |
|---|---|
| Administration of vitamin A | 9 |
| Pyretotherapy | 7 |
| Topical applications | 10 |
| Other treatment | 5 |

QUESTION 2.—*If there has been improvement, do you attribute it to any particular treatment you have received?*

This question was asked more from the standpoint of academic interest than with the expectation of gathering precise scientific information. However, as is shown in table 2, the replies do bring out one point very clearly, namely, that no single form of therapy appears to be specific in the treatment of all forms of pityriasis rubra pilaris. The three most generally used forms of treatment—vitamin A (usually given orally, occasionally given parenterally), pyretotherapy (by means of pilocarpine-induced sweats, "hypertherm" apparatus or injection of foreign protein) and topical applications (usually of coal tar or salicylic acid preparations)

8. Andrews, G. C.: Diseases of the Skin, ed. 3, Philadelphia, W. B. Saunders Company, 1946, p. 207.

—ranked approximately equal in the patients' estimation of their relative therapeutic value. "Other treatment" included faith healing, chiropractic treatments and the consumption of large quantities of vegetable soup.

QUESTION 3.—*Have you experienced any muscle weakness such as difficulty in walking, rising or eating or other forms?*

This question was asked primarily in an attempt to ascertain whether Mellanby's [6] observations might bear clinical import in these patients. Six of the patients noted the presence of some neuromuscular dysfunction. It is interesting that all these patients presented their complaints at the time that they were seen at the clinic. No further positive replies were elicited in response to the questionnaires in the course of the follow-up studies. A brief description of these cases follows:

CASE 1.—In June 1944, the patient, a white woman 32 years old, experienced some transient urticarial lesions, after which she noticed swelling and subsequent fissuring of the hands. This same condition later spread to the legs, arms and abdomen. In January 1946 pronounced lichenification of the palms and soles developed and persisted to the date of her first admission to the clinic in January 1947. She noted the onset of progressive muscular weakness in July 1946 and had lost 60 pounds (27 Kg.) in a period of two years. On admission to the clinic, the patient presented a generalized erythroderma with decided lichenification of the palms and soles. The clinical diagnosis of pityriasis rubra pilaris was made here and also previously by two competent dermatologists. A biopsy specimen of the skin at this time was interpreted as showing pityriasis rubra pilaris. Since then, the condition of the skin has remained approximately the same, with minor remissions and exacerbations, but the weakness has become progressively worse and atrophy of some groups of muscles, particularly about the shoulder girdle, has appeared. Observations on biopsy of muscle in September 1948 were considered as being "consistent with dermatomyositis." At the same time, roentgenographic studies of the bones of the hands showed changes consistent with a diagnosis of acrosclerosis and a roentgenogram of the thorax revealed fibrosis consistent with scleroderma. Since then, the patient's skin has shown poikiloderma-like changes and the muscular changes have continued to progress, so that, at the time of writing, a clinical diagnosis of "sclerodermatomyositis" seems most proper.

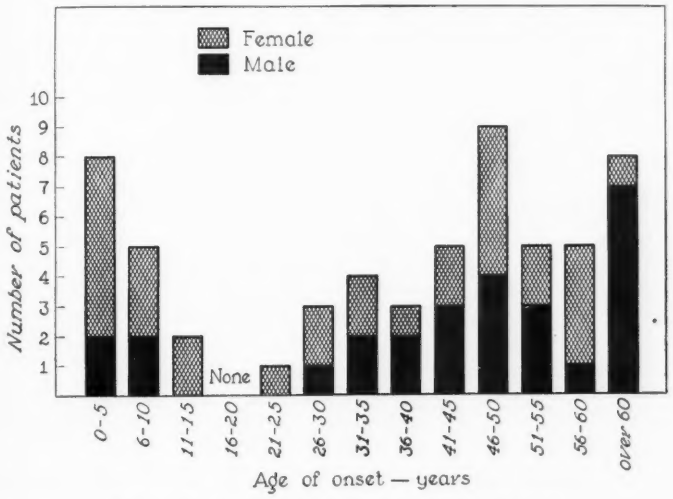
CASE 2.—The patient, a boy 10 years old, first noticed the onset of generalized muscular weakness, particularly difficulty in walking and eating, in September 1945. In November 1945, a diagnosis of myasthenia gravis was made and treatment with neostigmine bromide was instituted, after which therapy the patient's symptoms were somewhat relieved. At the same time erythematous, scaling lesions developed in both axillas, crusted lesions appeared in the scalp and thickened, lichenified, scaling patches of dermatitis manifested themselves on the knees, elbows, palms and soles. A diagnosis of pityriasis rubra pilaris was made. On the patient's admission to the clinic, in January 1946, physical examination revealed generalized muscular weakness, grade 2 (on a basis of 1 to 4) and the cutaneous eruption. Since then, the neuromuscular and cutaneous symptoms have persisted, except for occasional remissions and exacerbations of both.

CASES 3 TO 6.—These 4 patients complained of generalized muscular weakness of undetermined origin which began, respectively, three years prior to, one year

prior to, four months prior to and one year after the onset of the cutaneous lesions of pityriasis rubra pilaris. Physical examination, however, revealed no objective evidence to account for the weakness of which these patients complained.

### AGE AT ONSET

Discussing a case of pityriasis ruba pilaris presented by Cornbleet and Cohen before a meeting of the Chicago Dermatological Society, O'Leary [9] stated that it was his belief that actually two forms of the disease existed, that form associated with night blindness and helped by vitamin A therapy and that in which night blindness is not present and which is not helped by treatment with vitamin A.




Age at onset of pityriasis rubra pilaris in 58 cases.

This premise is well borne out by data on the age at onset in our 58 cases shown in the accompanying figure. It can be seen that the patients fall into one of two groups, quite readily, on the basis of their age at the time of the onset of the disease. Giving further credence to this idea is the report by Leitner [4] of 6 cases of the disease with familial tendency in each. Every one of his patients first showed manifestations of the disease in infancy or childhood. Ford [10] analyzed Leitner's

9. O'Leary, P. A., in discussion on Cornbleet, T., and Cohen, D.: Pityriasis Rubra Pilaris: Case for Diagnosis, Arch. Dermat. & Syph. **47**:463-464 (March) 1943.

10. Ford, E. B.: The Genetics of Pityriasis Rubra Pilaris, in Leitner and Ford,[4] pp. 424-426.

cases genetically and expressed the opinion that the familial form of pityriasis rubra pilaris is inherited as a simple autosomal, heterozygous condition.

Zeisler [11] also differentiated pityriasis rubra pilaris into two groups: a mild familial type and a severer acquired form. Sutton's discussion of Zeisler's report well brought out the practical importance of determining which form of the disease is present in a given patient, especially with regard to the question of whether the patient's children might also have the disease. In only 1 case in our series of 58 were we able to elicit a definite familial history of pityriasis rubra pilaris in a female patient, who first manifested the disease at the age of 3 months. A perusal of the literature revealed no evidence of genetic transmission of the form of pityriasis rubra pilaris which appears in adulthood.

Only five replies to questionnaires were received from 15 patients in whom the disease began during childhood. Of these, 1 claimed to be completely free of lesions, 3 said that the condition had improved and 1 replied that there was no change.

## SUMMARY AND CONCLUSIONS

A clinical analysis of 58 cases of pityriasis rubra pilaris was made. Thirty-one of the patients answered questionnaires sent from one to twenty-one years after the diagnosis had been made. In 5 of these patients the disease had developed in childhood. Of the patients who replied to questionnaires, all but 4 reported improvement in the cutaneous lesions or complete absence therefrom. Four of the patients who had acquired the disease in childhood had had improvement.

Opinion was about equally divided among these patients as to the relative therapeutic merits of vitamin A, topical applications and pyretotherapy.

Six patients in this group of 58 had symptoms of neuromuscular dysfunction. One had generalized weakness with muscular atrophy, 1 had myasthenia gravis and 4 patients had generalized muscular weakness which could not be explained on the basis of objective physical findings. We are of the opinion that the occurrence of neuromuscular disease in the first 2 patients in this group of 6 in this series was coincidental and unrelated to the condition of the skin.

The patients fall into two groups with regard to their age at the time of the onset of symptoms. One group first showed manifestations of the disease in infancy or childhood, and the other, in middle age.

There are probably two distinct types of pityriasis rubra pilaris, a familial type which has its onset in infancy or childhood and an acquired type which has its inception in middle age and shows no genetic relation.

11. Zeisler, E. P.: Pityriasis Rubra Pilaris—Familial Type, Arch. Dermat. & Syph. **7**:195-207 (Feb.) 1923.

# AUTOECZEMATIZATION

**Preliminary Report**

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THE SOLUTION of the problems of eczema depends on the correlation of many interrelated facts. One apparent connecting link is the process of autoeczematization, which develops in many types of eczematous dermatoses. Autoeczematization, as considered here, consists in the development of scattered eczematous lesions complicating an acute eczematous process ordinarily of limited extent.

Because of the paucity of experimental work on what is felt to be a fundamental and important problem, a study has been instituted of some of the mechanisms involved. This paper is a preliminary report of such studies.

## SURVEY OF THE LITERATURE

The concept of autoeczematization stems from the observations of Whitfield,[1] who postulated that a person might become sensitized to split products of autogenous tissue proteins. Whitfield described three types of reactions, one, and possibly two, of which fits into the present day concept of autoeczematization. The first consisted of widely distributed, papulovesicular patches, developing a number of days after an exacerbation of a chronic lichenified eczema. In the second type, a linear urticarial lesion followed by a papulovesicular eruption developed at points of contact with serum draining from an acute eczematous process. Third, Whitfield reported the development of a scattered, erythematous and urticarial eruption some ten days after the occurrence of traumatic hematomas.

Whitfield's first type, as previously described, is in general accord with present day conceptions of autoeczematization. The clinical features

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Read at the Sixty-Ninth Annual Meeting of the American Dermatological Association, Inc., at Hot Springs, Va., May 25, 1949.

1. Whitfield, A.: The Question of Sensitiveness to Non-Bacterial Toxins and Proteins, Brit. J. Dermat. **34**:331 (Nov.) 1922; Discussion on Eczema, Brit. M. J. **2**:332 (Aug. 21) 1926; Autosensitization in Eczema, in the transactions of the Eighth International Dermatological Congress, Copenhagen, 1930.

of this reaction were well delineated by Smith.[2] More recently, Templeton and his associates [3] discussed, with illustrative cases, the various types of dermatitis which may be complicated by this syndrome. Further examples of "autoeczematization" subsequent to hematomas have not been encountered in the literature. However, Bizzozero [4] reported the production of papules or wheals following injection of autogenous blood or serum in patients sensitized to those products. The development of urticaria from contact with serum from an eczematous source is likewise uncommon. Sutton's description [5] of generalized urticaria following infectious eczematoid dermatitis not only is unusual but also does not conform to Whitfield's original description of this type.

During recent years, attention has been centered, particularly by allergists, on the development of homologous sensitization to human dander in various eczematous and allergic processes. The early work on this subject has been well summarized by Hampton and Cooke.[6] In a provocative study, these investigators found that 30 of 33 patients with "allergic dermatitis" had skin reactions to human dander extract and, in addition, had skin-sensitizing antibodies in their serums. Patients with other allergic diseases, with dermatoses other than "allergic dermatitis" and normal controls reacted only exceptionally with this extract.

In a series of eight publications, Simon [7] described further studies on patients with atopic dermatitis and other allergic disorders and on normal controls. In his earlier work, with the utilization of normal

2. Smith, S.: Eczema Autolytica, Brit. M. J. **1**:628 (May 5) 1945.

3. Templeton, H.; Lunsford, C., and Allington, H.: Autosensitization Dermatitis: Report of Five Cases and Protocol of an Experiment, Arch. Dermat. & Syph. **59**:68 (Jan.) 1949.

4. Bizzozero, E.: Ueber die Sensibilisierung der Haut gegen das Eigenserum und das Eigenblut, Arch. f. Dermat. u. Syph. **173**:342, 1936.

5. Sutton, R.: Infectious Eczematoid Dermatitis, J.A.M.A. **75**:976 (Oct. 9) 1920.

6. Hampton, S., and Cooke, R.: The Sensitivity of Man to Human Dander, with Particular Reference to Eczema (Allergic Dermatitis), J. Allergy **13**:63 (Nov.) 1941.

7. Simon, F.: Skin Reaction to Patch Test with Human Dander, Ann. Allergy (March-April) 1944; On the Allergen in Human Dander, J. Allergy **15**:338 (Sept.) 1944; Human Dander: An Important Cause of Infantile Eczema, J.A.M.A. **125**:350 (June 3) 1944; Cutaneous Reactions of Persons with Atopic Eczema to Human Dander: Results of Patch Tests on Scarified Skin, Arch. Dermat. & Syph. **51**:402 (June) 1945; The Pathogenesis of Atopic Eczema, South. M. J. **38**:530 (Aug.) 1945; The Allergen of Human Dander Present in Skin of the General Body Surface, J. Invest. Dermat. **9**:329 (Dec.) 1947; The Allergen of Human Dander: Its Relative Concentration in Several Skin Areas and in Appendages, Products and Derivatives of the Epidermis, ibid. **11**:203 (Sept.) 1948; A Study of Atopic Eczema: I. Further Observations on Allergy to Human Dander; II. Cutaneous Reactions to Eczema Scales, Ann. Allergy **6**:584 (Sept.-Oct.) 1948.

scalp dander, positive immediate reactions to intradermal tests and delayed eczematous reactions to patch tests and patch on scratch tests were obtained in a significant proportion of cases. Dander from the general body surface was utilized in subsequent studies, and similar results were obtained. Moreover, antibody neutralization experiments indicated that scalp and general body dander contained a common antigen. In a final group of 24 patients with atopic dermatitis, approximately 50 per cent reacted positively to patch tests and patch on scratch tests to dander from eczematous lesions. It is of interest that positive reactions were obtained when scalp and body dander from a newborn infant were utilized. This would suggest that the reactions were not caused by bacterial contamination.

The literature contains many examples of the production in animals of sensitization to autogenous body tissues. Working with rabbits, Burky [8] produced sensitization to lens substance by repeated injection of this tissue mixed with staphylococcus toxin. The reaction was clinically manifested by an anaphylactic type of endophthalmitis when the lens was subsequently needled. In addition, the lens-sensitive rabbits were found to have high precipitin titers for lens substance. Similarly, Burky [8] showed that injections of staphylococcus toxin prepared in rabbit muscle broth resulted in sensitization to autogenous muscle products, as demonstrated by the development of a severe local reaction after the rabbit muscle was squeezed.

In additional experiments, brain, cord or kidney tissue was found by Schwentker and Rivers,[9] Masugi [10] and Smadel and Swift [11] to produce an organ-specific sensitization. It is of interest that Karady [12] apparently was able to produce anaphylactic reactions in guinea pigs following sensitization to autogenous blood serum which had been altered by previous heating or chilling.

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8. Burky, E.: Experimental Endophthalmitis Phaco-Anaphylactica in Rabbits, Arch. Ophth. **12**:536 (Oct.) 1934; Production of Lens Sensitivity in Rabbits by Action of Staphylococcus Toxin, Proc. Soc. Exper. Biol. & Med. **31**:445 (Jan.) 1934; Production in Rabbit of Hypersensitive Reactions to Lens, Rabbit Muscle and Low Ragweed Extracts by Action of Staphylococcus Toxin, J. Allergy **5**:466 (July) 1934

9. Schwentker, R., and Rivers, T.: Antibody Response of Rabbits to Injections of Emulsions and Extracts of Homologous Brain, J. Exper. Med. **60**:559 (Nov.) 1934.

10. Masugi, M.: Ueber die experimentelle Glomerulonephritis durch das spezifische Antinierenserum: Ein Beitrag zur Pathogenese der diffusen Glomerulonephritis, Beitr. z. path. Anat. u. z. allg. Path. **92**:429, 1934.

11. Smadel, J., and Swift, H.: Reverse Anaphylaxis in Rats, with Special Attention to Kidney Damage, J. Immunol. **32**:75 (Jan.) 1937.

12. Karady, S.: Role of Auto-Antigens in Pathogenesis of Physical Allergy, J. Immunol. **37**:457 (Nov.) 1939.

From Burky's original work, Hopkins and Burky [13] hypothesized that chronic eczemas of the hands might be due to autogenous sensitization to dander, the reaction being potentiated by secondary staphylococcic invasion. Gratifying therapeutic results were obtained when repeated injections of staphylococcus toxin were given to patients with this type of eczema.

Additional evidence that circulating antibodies may develop during sensitization to homologous dander was presented by Hecht, Sulzberger and Weil.[14] These authors, working with rabbits, administered a single intramuscular injection of homologous skin antigen and repeated intradermal injections of staphylococcus toxin. This procedure resulted in the formation of precipitins to the homologous skin antigen. Precipitin reactions were slight or absent when skin antigen alone was used. Somewhat similar experiments were performed in human beings by the Templeton group.[3] A homologous whole skin extract was injected into 5 normal subjects, either intradermally or subcutaneously, for a total of three to four injections in either a four day or sixteen day period. Precipitins to the antigen were identified in the serum of all 5 subjects on the sixteenth day. Control precipitin tests gave negative reactions.

## MATERIALS AND METHODS

Thirty patients were utilized in the present study. All but 3 of these had active autoeczematization. The remaining 3 were patients with atopic dermatitis, the eruption of which was complicated by distal lesions resembling autoeczematization. In all cases with distal eczematization the condition developed as a complication of an acutely inflamed, localized cutaneous lesion. The original dermatoses were of the following primary types: contact dermatitis, stasis eczema, seborrheic dermatitis, nummular eczema and atopic dermatitis. It should be emphasized, however, that in many instances multiple etiologic factors were present. For example, a stasis eczema might be complicated by secondary infection, on which was superimposed a primary irritant effect or a true allergic contact dermatitis from medication. In some cases the development of autoeczematization was accelerated by excoriations due to pruritus associated with neurogenous factors. In the reporting of the experiments, the patients were classified according to the type of dermatitis which was considered most important in the production of the autoeczematous reaction.

The following test substances were used: (*a*) extract of scales (dander), (*b*) blood plasma, (*c*) suspension of blood leukocytes and (*d*) blister fluid. It should be emphasized at this point that each patient was tested only with products of his

13. Hopkins, H., and Burky, E.: Cutaneous Autosensitization: Role of Staphylococci in Chronic Eczema of the Hands, Arch. Dermat. & Syph. **49**:124 (Feb.) 1944.

14. Hecht, R.; Sulzberger, M., and Weil, H.: Studies in Sensitization to Skin: I. The Production of Antibodies to Skin by Means of the Synergistic Action of Homologous Skin Antigen and Staphylococcus Toxin, J. Exper. Med. **78**:59 (July 1) 1943.

own tissues. A few homologous tests were performed in the control series, as later described. In the first 24 cases, tests were made with crude scale extract, blood plasma and blood leukocyte suspension.

*Preparation of Crude Scale Extract.*—A relatively hairless site was prepared with 70 per cent ethyl alcohol. In the first 8 cases the flexor surface of the arm or forearm was utilized, while in the remaining 16 an area adjacent to the site of the primary dermatitis was chosen. Scales were obtained by gentle curettement with a sterile scalpel. The scales were then placed in a sterile glass vial containing an isotonic solution of sodium chloride. After one hour, the suspension was aspirated into a sterile tuberculin syringe preparatory to injection. One cubic centimeter of the sodium chloride solution was used in the first sixteen experiments and 0.5 cc. in the remaining eight. The total quantity of scales used was not precisely determined but was kept relatively constant.

*Extraction of Plasma and Leukocytes.*—Blood, 10 cc., was withdrawn from an antecubital vein and placed in a sterile flask containing 1 cc. of heparin (5 mg. per cubic centimeter). The blood was centrifuged, using sterile precautions, at 1,000 r.p.m. for fifteen minutes. The supernatant plasma was withdrawn into a tuberculin syringe for the test injection. The buffy coat, admixed with some red cells, was then removed by pipet and placed in a Hopkins tube, the bottom inch (2.5 cm.) of which has a narrow bore. This material was then recentrifuged for fifteen minutes, whereupon a pure buffy coat was removed with a capillary pipet. Stained smears of this material in controls demonstrated that it consisted of a nearly pure extract of leukocytes, admixed with small numbers of thrombocytes, red cells and fat globules. The extracted buffy coat was then suspended in a sterile isotonic solution of sodium chloride. As with the scales, 1.0 cc. of sodium chloride solution was used in the first sixteen experiments and 0.5 cc. in the remaining eight.

*Modified Preparation of Test Substances.*—For reasons which will be later discussed, further modifications were used in the last six cases for the preparation of the scale extract. In this same group, blood for plasma and leukocyte extracts was obtained, whenever possible, from a vein draining the primary inflammatory site. Blister fluid obtained from skin adjacent to this site was used as an additional test substance. The method of extraction of blood plasma and leukocytes was identical to that previously described.

As in the previous experiments, scales were obtained from skin adjacent to the primary area of dermatitis. The scales were washed four times with ether, and the ether washings were discarded. The scales were then suspended in 0.5 cc. of a sterile isotonic solution of sodium chloride for forty-eight hours. After this step the supernatant fluid was withdrawn and phenol to make a final concentration of 0.45 per cent was added, preparatory to the test injection. In the first 2 cases tested, the fluid was diluted 1:10 after the method of Simon,[7] while in the last 4 cases it was used undiluted.

Blister Fluid: The blister was produced by the application of a ½ inch (1 cm.) square of cantharides plaster, which was kept in place for twenty-four hours. The blister fluid was then removed under sterile precautions for the test injection.

*Performance of Tests.*—For the test injections, 0.1 cc. of each substance was administered intradermally. The test site was ordinarily the flexor surface of the arm or forearm, but when these areas were involved by the eczematous process a site on the upper portion of the back was used. An isotonic solution of sodium chloride was employed for all control injections. Immediate reactions were read in ten to thirty minutes, depending on the time of development of the maximal reaction. The sites were reexamined for delayed reactions after the elapse of forty-eight hours.

*Controls.*—Eighteen control experiments were done, plasma and leukocyte suspension being utilized in nine instances, crude scale extract in eleven and modified scale extract in seven.

## RESULTS OF EXPERIMENTS

As can be seen in the accompanying table, reactions were encountered most commonly with scale extracts. There were 14 positive and 1 doubtful immediate reactions, and 10 positive and 1 doubtful delayed reactions. However, when these results are further analyzed, it will be seen that only 11 out of 24 persons (46 per cent) had positive immediate reactions and 7 out of 24 (29 per cent) had positive delayed reactions to crude

*Immediate and Delayed Reaction to Injections of Various Substances*

| Primary Reactions Type | No. of Cases | Immediate Reactions | | | | Delayed Reactions | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Plasma | Leukocyte Suspension | Scale | Blister Fluid | Plasma | Leukocyte Suspension | Scale | Blister Fluid |
| Contact dermatitis | | | | | | | | | |
| A * | 12 | 0 | 2 | 4 | — | 1± | 2± | 3 | — |
| B † | 3 | 0 | 2 | 2 | 2 | 1 | 0 | 2 | 0 |
| Stasis eczema | | | | | | | | | |
| A * | 5 | 1 | 2 | 3 | — | 0 | 0 | 1 | — |
| B † | 3 | 0 | 1 | 2 | 2 | 0 | 1± | 1, 1± | 0 |
| Seborrheic dermatitis | 1 | 1 | 0 | 1± | — | 0 | 0 | 0 | — |
| Nummular eczema | 3 | 0 | 0 | 0 | — | 0 | 0 | 1 | — |
| Atopic dermatitis | 3 | 1 | 2 | 3 | — | 0 | 0 | 2 | — |
| Totals | 30 | 3 | 9 | 14, 1± | 4 | 1, 1± | 3± | 10, 1± | 0 |
| Control—plasma, leukocyte suspension, crude scale | 9 | 4 | 2 | 0 | — | 0 | 0 | 0 | — |
| Control—additional crude scale | 2 | — | — | 0 | — | — | — | 0 | — |
| Control—modified scale (undiluted) | 7 | — | — | 0 | — | — | — | 0 | — |

* Crude scale extract, blood from antecubital vein.
† Modified scale extract, blood from vein draining inflammatory site, blister fluid.

scale extract. When the diluted (1:10) modified scale extract was employed in 2 cases, no reactions were obtained. On the contrary, when the undiluted modified scale extract was used, there were 4 out of 4 (100 per cent) persons with positive immediate reactions and 3 with positive and 1 with doubtful delayed reactions in these 4 (75 per cent). No reactions to scale extracts were obtained in controls, even when the undiluted modified scale extract was employed.

Nine positive immediate (30 per cent) and 3 doubtful delayed reactions were obtained with leukocyte suspensions. Two out of 9 control patients had positive immediate reactions (22 per cent).

Of the 30 patients tested with plasma, 3 had positive immediate reactions (10 per cent), while 1 positive delayed reaction and 1 doubtful delayed reaction were obtained. There were 4 positive immediate reactions among the 9 controls (44 per cent).

Four out of 4 patients tested with blister fluid had positive immediate reactions. The significance of these reactions remains in doubt since control tests have not yet been performed.

The small number of cases of each type of primary reaction precludes any comparison of the relative frequency of reactions in the different types.

*Description of Reactions.*—A positive immediate reaction consisted of a central wheal and a surrounding erythematous flare and is illustrated in figure 1.

The positive delayed reaction was obtained, with but one exception, only to scale extract. It consisted of a raised, red, firm papule, varying

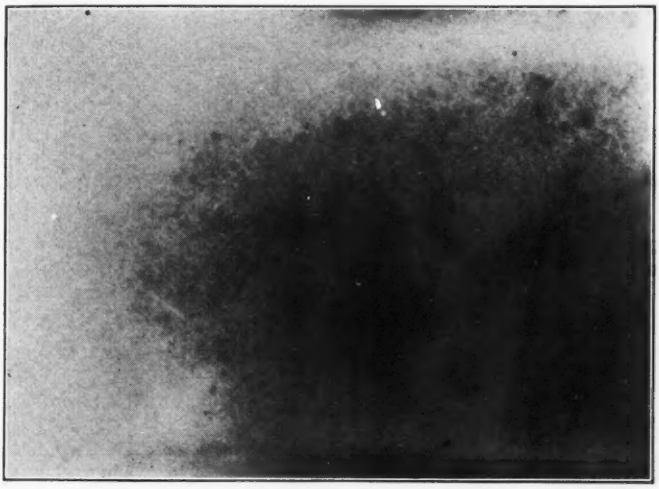

Fig. 1.—Immediate type of reaction to scale extract. This reaction was identical with those obtained with other test substances.

in diameter from 3 to 9 mm., with an average of 6 mm. It is of interest that with 3 reactions a surrounding erythematous flare of from 7 to 30 mm. was present. A typical delayed reaction is illustrated in figure 2.

A biopsy specimen was obtained from the area of a positive delayed papular reaction to scales. The histopathologic observations were reported by Dr. Wilbert Sachs as follows:

> The vessels of the midcutis and upper portion of the cutis were dilated, and the walls were somewhat thickened. About the vessels was a pronounced focal infiltration of small round cells, wandering connective tissue cells and numerous polymorphonuclear leukocytes including eosinophils. There was considerable interstitial edema throughout the entire cutis. The epidermis was slightly acanthotic; the palisade layer was intact, and the granular and horny layers were distinct. There was no edema of the epidermis. The diagnosis was neurodermatitis reaction.

## IMMUNOLOGIC MECHANISMS IN AUTOECZEMATIZATION: PRELIMINARY DISCUSSION OF POSSIBLE ALLERGIC NATURE

The mechanism involved in autoeczematization, as interpreted by observation of the clinical development, has a significant resemblance to that of an allergic reaction as defined by von Pirquet. In autoeczematization it is assumed that an antigenic substance is elaborated at the site of an acute primary eczematous focus. If this primary inflammatory focus persists unabated for a minimal period of seven to fourteen days, it may be postulated that the continual absorption of antigenic material is constantly stimulating the formation of antibodies. Further

Fig. 2.—Positive forty-eight hour reaction to scale extract.

absorption of antigen then leads to the development of secondary eczematous lesions at distant sites. After the subsidence of this reaction, a recurrence of the primary inflammatory focus or the development of a severe localized dermatitis from other causes may result again in distal eczematization.

Experimental confirmation of the immunologic mechanisms involved in this concept should include the following studies. A primary prerequisite is the positive identification of the antigen. A study should then be made of the conditions in which it is formed and disseminated. The mode of transport of the antigen from the primary site may next be investigated. It would be desirable also to know the site of antibody formation, whether it be in the skin or in the reticuloendothelial system,

and in the latter event to ascertain its method of transport to distant cutaneous areas. Finally, the nature of the antigen-antibody reaction remains to be determined.

### COMMENTS ON EXPERIMENTAL STUDIES

In the studies herein reported, an attempt has been made to clarify some of the mechanisms involved in autoeczematization. In an initial experiment, plasma, leukocyte suspensions and a crude scale extract were used as the test substances. As the work developed, however, certain modifications in the investigative procedures were imposed by the results obtained. These modifications will be discussed in the comments on the individual experiments.

In the preliminary experiment, the employment of plasma as a test substance resulted in but few reactions (for the most part immediate), the specificity of which was doubted because of the frequency of reactions in controls. It would seem, then, that either the antigen was not transported in the plasma or, if so, it was present in quantities too small to be detected by skin testing. More reactions were obtained with the leukocyte suspension, and it may be that the antigen is transported by these cells. However, the relative frequency of reactions in controls militates against this assumption. The use of the crude scale extract resulted in a surprising number of reactions (46 per cent immediate, 29 per cent delayed) when the relatively inefficient method of extraction of the scales is considered. Also noteworthy is the fact that this crude suspension of scales failed to give any positive reactions in controls, even though small scale particles were almost certainly injected. During the course of the experiment it was deemed advisable to increase the concentration of the leukocyte suspension and scale extract in an attempt to obtain a greater percentage of positive reactions. No significant difference in frequency of reactions was noted. It was felt that the collection of scales from a site adjacent to the primary eczematous focus might provide a more potent antigen. This assumption was not substantiated by the results obtained, but the method was continued throughout the later experiments. In order that undue bacterial contamination might be avoided, the primary focus was not used as a source of scale extract.

In the modified experiments, a further refinement in the preparation of scale extract was introduced. When this forty-eight hour extract of ether-washed scales was used in the proper concentration in a small series, the percentage of positive immediate reactions rose to 100, and that of positive delayed reactions to 75. Of special significance was the fact that none of 7 additional control patients reacted to this extract. This would seem to obviate the necessity of dialysis as recommended by some investigators.[6] Additional control experiments will be performed

to support this belief. When the leukocyte suspension was obtained from venous blood draining the primary inflammatory site, the percentage of immediate reactions to leukocytes was doubled (50 in comparison with 25 per cent). If the antigen is transported by leukocytes, this finding would suggest that it is present in greater concentration in venous drainage of the primary site than in distant venous blood.

Blister fluid was used as a possible additional source of epidermal antigen, since the antigen may be concentrated in this fluid during its transudation through epidermal cells injured by a cantharides plaster. On examination, leukocytes were not found in the blister fluid. The development of immediate reactions in all 4 persons tested to blister fluid would seem to substantiate further the existence of a specific water-

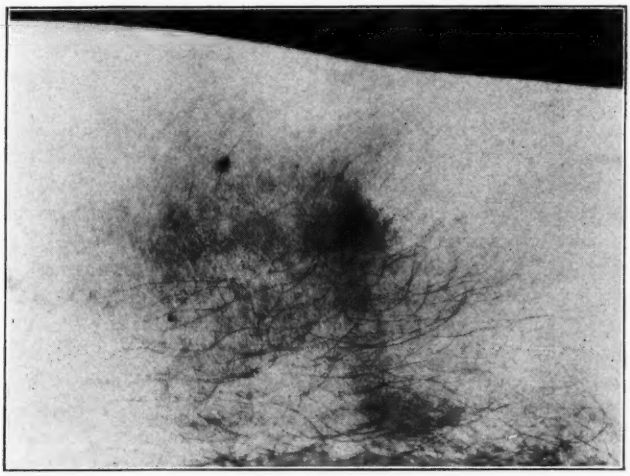

Fig. 3.—Spontaneous flare reaction to injection of homologous leukocytes.

soluble epidermal antigen. Further studies to confirm this point are in progress.

An interesting phenomenon was observed in the course of a control experiment with homologous test substances. Fourteen days after an initial injection of homologous leukocyte suspension, an erythematous papule 10 mm. in diameter developed in the injection site. Since this reaction seemed to correspond to the spontaneous flares observed frequently during the course of a developing sensitization, a second injection, in another site, was given twenty-eight days after the initial one. This resulted, after forty-eight hours, in the development of an erythematous papule 5 mm. in diameter. An identical result was obtained after a further injection was given at a later date. The spontaneous flare reaction is illustrated in figure 3.

## THEORETIC IMPLICATIONS OF PRESENT EXPERIMENTS AND WORK OF PREVIOUS INVESTIGATORS; CORRELATION WITH CLINICAL OBSERVATIONS

The results obtained in the present experimental study point to the existence of a specific antigen in the autoeczematous reaction and further indicate its close relation to a water-soluble component of epidermal cells. On the basis of clinical observations, autogenous epidermal cells may become antigenic in the presence of a severe inflammatory process under certain conditions. During the course of an acute vesicular or exudative reaction, the superficial epidermal structures are bathed in vesicular fluid or exuding serum, the absorption of the antigen into the general circulation (see comment on possible antigenicity of blister fluid) thus being permitted. Furthermore, the invasion of leukocytes into edematous epidermis releases proteolytic enzymes which in turn accelerate the breakdown of epidermal cells and facilitate their absorption. Chemical irritation and mechanical trauma such as excoriation enhance

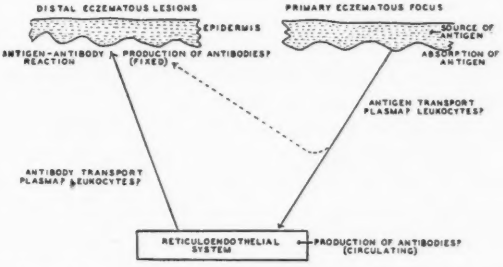


Fig. 4.—Schematic representation of possible mechanisms in autoeczematization.

this process; their influence has been observed repeatedly in the evolution of the clinical reaction. Roentgen radiation therapy of an acute eczematous process not infrequently results in autoeczematization; the mechanism of this action may be through the sudden release of proteolytic enzymes from destroyed leukocytes.

The transportation of antigen (by leukocytes) to the site of antibody formation (reticuloendothelial system) was apparently demonstrated by Sabin [15] by tracer studies with dye-protein antigen. More recently, Godlowski [16] reported that antigen is transported only by eosinophilic leukocytes. The present studies, while incomplete in many respects, suggest that leukocytes (and not plasma) have a comparable role in the transport of antigen in the development of autoeczematization.

15. Sabin, F.: Cellular Reactions to a Dye Protein with a Concept of the Mechanism of Antibody Formation, J. Exper. Med. **70**:67 (July) 1939.

16. Godlowski, Z.: Transportation of the Anaphylactogenic Property by Eosinophils, Brit. J. Exper. Path. **29**:511 (Dec.) 1948.

Nothing can be said at this time regarding the site of formation and transportation of the antibodies. It is likely, however, that the antibody is formed in some portion of the reticuloendothelial system, possibly the lymph nodes. More improbably, it may be formed in the skin itself. The problem then arises as to the nature of the antibody. However, a consideration of the type of intradermal reactions obtained to scale extract in this experiment may throw some light on its nature. It is well known that the immediate reaction is associated with the presence of circulating antibodies. Such antibodies apparently have been demonstrated following injection of skin extracts in the experimental animal by Hecht and his co-workers [14] and in normal human subjects by Templeton and his associates.[8] The previously unreported delayed reactions observed in the present experiments suggest that a sessile (fixed cellular) antibody may be present as well.

On the basis of the previous comments, a diagrammatic representation of possible mechanisms in the autoeczematous process is presented in figure 4.

## DIRECTION OF FUTURE RESEARCH IN AUTOECZEMATIZATION

There remain for consideration some problems toward which further investigation should be directed. In the first place, the specificity of the scale antigen should be confirmed, and its more complete purification attempted. Confirmation is necessary on the role of the leukocytes in the transportation of antigen, and the importance of the eosinophil in this process should be evaluated. Information concerning antibody formation and transport may be obtained by passive transfer experiments, neutralization studies and identification of precipitins. The utilization not only of the intradermal test but also of the patch test as used by Simon [7] in his work on atopic dermatitis may be useful for the detection of fixed antibodies. The Urbach-Koenigstein test might also be utilized for this purpose.

Concerning the site in the skin of the antigen-antibody reaction, the technic of Warren and Dixon [17] may yield interesting observations. As applied to this problem, the technic would involve the radioactive tagging of epidermal antigen and the identification of the site of its collection in the antigen-antibody reaction by means of a combined radiographic-histologic determination.

Information regarding the conditions under which the antigen is liberated from the primary site may be obtained by detailed pathologic studies of this site before and during the process of autoeczematization.

17. Warren, S., and Dixon, F.: Antigen Tracer Studies and Histologic Observations in Anaphylactic Shock in the Guinea Pig, Am. J. M. Sc. **216**:136 (Aug.) 1948.

Other factors influencing the liberation of antigen may include secondary bacterial infection and contact sensitization and they require further consideration.

Finally, is it possible to apply the knowledge of the mechanisms involved in the concept of autoeczematization to possibly related but clinically distinct processes such as atopic dermatitis, nummular eczema, seborrheic dermatitis and the recalcitrant eczematous lesions of the hands? If a common immunologic mechanism can be identified, a significant advance toward the unraveling of the enigma of eczema may be made.

SUMMARY

Data on a preliminary study concerning the nature of autoeczematization are reported here.

Autoeczematization is considered to be a true allergic reaction.

The antigen responsible for the distal eczematous response is apparently a water-soluble fraction of epidermal cells.

The development of immediate and delayed responses to intradermal injection of the antigen suggests that both fixed and circulating antibodies are present.

Homologous sensitization to human leukocytes is described.

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## ABSTRACT OF DISCUSSION

DR. HARRY J. TEMPLETON, Oakland, Calif.: I am very pleased to have the opportunity to discuss Dr. Cormia's paper because of my associates and my interest in this subject for many years.

Prior to the advent of Whitfield's concept, our thinking concerning the acute dissemination of a localized eczema was very hazy. We knew that an old eczema of the leg could suddenly flare up, this exacerbation being followed by generalized patches of papulovesicular dermatitis of varying degree and extent. However, it was not until we became familiar with Whitfield's idea that we began to understand the mechanism underlying the reaction.

Since then we have sought and found this mechanism to be involved in a number of the obscure eczema problems we encountered. So frequently do we see various examples of this phenomenon (I should say several times a month) that we feel that Whitfield's concept has become a valuable addition to our way of thinking in everyday practice. It is not only a theoretic approach; it is a very practical one.

The most commonly seen example of this reaction is probably due to an antigen conjugated from tissue juices at the primary site of eczema and local medication. The classic example is the case of an elderly patient with leg eczema of long duration, with or without ulceration. After injudicious local medication with sulfonamide ointments, iodine, ammoniated mercury or the like, the primary eczema exacerbates and then, in about a week, generalizes. We have seen a number of such reactions, basically the same, from industrial burns and injuries which had been treated with sulfathiazole ointment. All such reactions are probably related to Dennie's cases caused by what he called "protein picrinate."

Another occasionally seen variety probably comes from a tissue bacteria conjugated antigen; for example, the old case of eczema of the leg which flares up and spreads without any history of local medication but with visible evidence of gross bacterial infection.

It is more difficult to prove the existence of autosensitization from unaltered eczema tissue products, as we cannot be certain that no bacteria are involved. But local exacerbation and then generalization which we have seen occur following injury of a relatively clean, nontreated eczema of the leg causes us to believe that this autosensitization exists. Experimental support of this clinical belief would seem to come from Dr. Allington's experiments showing the presence of precipitins following injections of skin extracts and Dr. Cormia's demonstration of sensitization following injection of epidermal scales.

I might question the wisdom of the substitution of the term "autoeczematization" for Whitfield's older term "autosensitization." Sensitization, which Dr. Cormia has demonstrated in his investigations, is a very definite thing, whereas eczematization is a loose term which means different things to different doctors.

As Dr. Cormia points out, there are many fascinating studies which should be made of this problem. One has to do with the role of bacteria in the conjugated antigens. The original site of eczema could be cultured, the many bacteria isolated and an antigen for intradermal testing made from each one by the Kruger method.

I hope that Dr. Cormia continues his studies and that his fine paper stimulates us to do likewise.

DR. MARTIN F. ENGMAN JR., St. Louis: I was particularly interested in Dr. Cormia's paper and also in Dr. Templeton's discussion. It seems to me, without accurate statistics at hand, that secondary eczematization occurs in about one fourth of the cases in which there is an acute dermatitis in some part of the body. It makes very little difference in what part. The secondary eruption seems to follow even though the acute or primary dermatitis has begun to improve.

The mechanism of the secondary eruption is not well understood. The majority of dermatologists seem to believe it is an allergic response. I prefer to look at it as a toxic reaction. Toxic products may be absorbed from the site of the acute inflammation, and a toxic rash may occur at various widely disseminated parts of the body. The evidence in favor of an allergic basis is not strong. Further studies of this phenomenon may be very enlightening.

DR. JACOB H. SWARTZ, Boston: I should like to ask Dr. Cormia whether he has done any work on nonpathogenic bacteria. There are much more accurate methods than just intradermal testing. When there is a nonspecific or toxic eruption, we always look for a focus of infection. How many bacteria are really nonpathogenic? I should be interested in hearing of work along that line.

DR. CHARLES C. DENNIE, Kansas City, Mo.: I was particularly interested in this subject as I have done some work along this line. There are certain types of this condition that occur after the application of local anesthetics or in the injections of those substances for prolonged anesthesia. The substances that give the most trouble are the ones containing the quinoline derivatives. In certain cases, a generalized reaction as well as a local one is produced in a very few hours. In 1 case the administration of this specific anesthetic produced a scarlatiniform eruption within twenty-four hours. Extreme edema occurred on the extremities, and the eyes were swollen shut. Paraaminobenzoic acid was given by mouth. The eruption disappeared within a very few days. Since the skin was dry, oil was applied. In three days the eruption became as severe as it was in the

beginning. It was found that oil containing hydroquinone had been used. The administration of paraaminobenzoic acid immediately stopped the eruption.

DR. JOHN GODWIN DOWNING, Boston: I believe that autosensitization is not a clearcut picture to most physicians. A different entity is meant when one speaks of an eruption following the local application of drugs or local bacterial infection. Autosensitization is a very distinct entity, and only a few true cases are seen. Whitfield originally described a bedridden patient who presented an oozing varicose eczema of the lower leg. The serum from the affected area dripped down over the intact skin and caused streaks of eczematous dermatitis. I recently saw a case of untreated acute seborrheal dermatitis in a bedridden patient with cardiac disease, who sat upright because of dypsnea. Similar streaks occurred from the serum's dripping down the neck and over the back.

DR. JOHN H. STOKES, Philadelphia: I should like to congratulate Dr. Cormia on his approach to a question which has daily importance for us. It will help explain certain of the elements which enter into the confused background. I believe that Whitfield's concept of sensitization is better than that of eczematization. The bacterial factor has not been considered in Dr. Cormia's work so far. Sensitization can be produced by autogenous extracts, for instance, pieces of one's own skin which, of course, contain many varieties of bacteria as well as one's own proteins. If one inoculates the suspended skin into one's own skin, a week later an autosensitivity reaction develops.

DR. FRANK E. CORMIA, New York: I am grateful for the kind words of the discussers. In reply to Dr. Engman's remarks, I might say that our preliminary study at least would indicate that the autoeczematization reaction occurs not only in the epidermis but also around blood vessels. In reply to Dr. Swartz's question, no work on nonpathogenic bacteria has been done. Dr. Dennie emphasizes the fact that there are many factors to be investigated in this very complicated process. I have no answer for Dr. Downing's comments. In regard to Dr. Stokes's remarks, we have not yet investigated the factor of bacterial sensitization as applied to this subject. I should like to call attention to the work of Simons, who found that he could obtain positive reactions in atopic subjects to a scale extract prepared from a newborn baby. In this situation, the factor of bacterial contamination would appear to be minimized.

# RESIN OF PODOPHYLLUM IN TREATMENT OF CANCEROUS AND PRECANCEROUS CONDITIONS OF SKIN

## Effect on Basal Cell Epithelioma and Seborrheic, Senile and Radiation Keratoses

LESLIE M. SMITH, M.D.
AND
H. D. GARRETT, M.D.
EL PASO, TEXAS

CHEMOTHERAPY of cutaneous cancer and precanceroses has received slight attention in the past. Sherwell's method [1] of treating basal cell tumors by curettage followed by the application of mercuric nitrate enjoyed a degree of popularity for a while and is still used occasionally by a few dermatologists. Recently, Mohs [2] advocated a technic utilizing an old remedy, zinc chloride, in which successive applications are made and the tumor tissue fixed by the drug is removed and studied microscopically before each new application. Both these methods depend on nonselective destruction of tissue.

The work of Kaplan [3] and others on the successful treatment of condyloma acuminata with resin of podophyllum and the studies of Sullivan and King [4] on the microscopic changes resulting from the use of colchicine and resin of podophyllum caused us to wonder about the practicability of employing these drugs in the treatment of epithelial growths other than condyloma. Ormsbee, Cornman and Berger [5] noted a selective damaging effect of resin of podophyllum on mouse tumor cells in tissue cultures.

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Read at the Sixty-Ninth Annual Meeting of the American Dermatological Association, Inc., at Hot Springs, Va., May 26, 1949.

1. Sherwell, cited by Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 9, St. Louis, C. V. Mosby Company, 1935.

2. Mohs, F. E.: Chemosurgical Treatment of Cancer of the Face: A Microscopically Controlled Method of Excision, Arch. Dermat. & Syph. **56**:143 (Aug.) 1947.

3. Kaplan, I. W.: Condyloma Acuminata, New Orleans M. & S. J. **94**:388 (Feb.) 1942.

4. Sullivan, M., and King, L. S.: Effects of Resin of Podophyllum on Normal Skin, Condylomata Acuminata and Verrucae Vulgares, Arch. Dermat. & Syph. **56**:30 (July) 1947.

5. Ormsbee, R. A.; Cornman, I., and Berger, R. E.: Effect of Podophyllin on Tumor Cells in Tissue Culture, Proc. Soc. Exper. Biol. & Med. **66**:586 (Dec.) 1947.

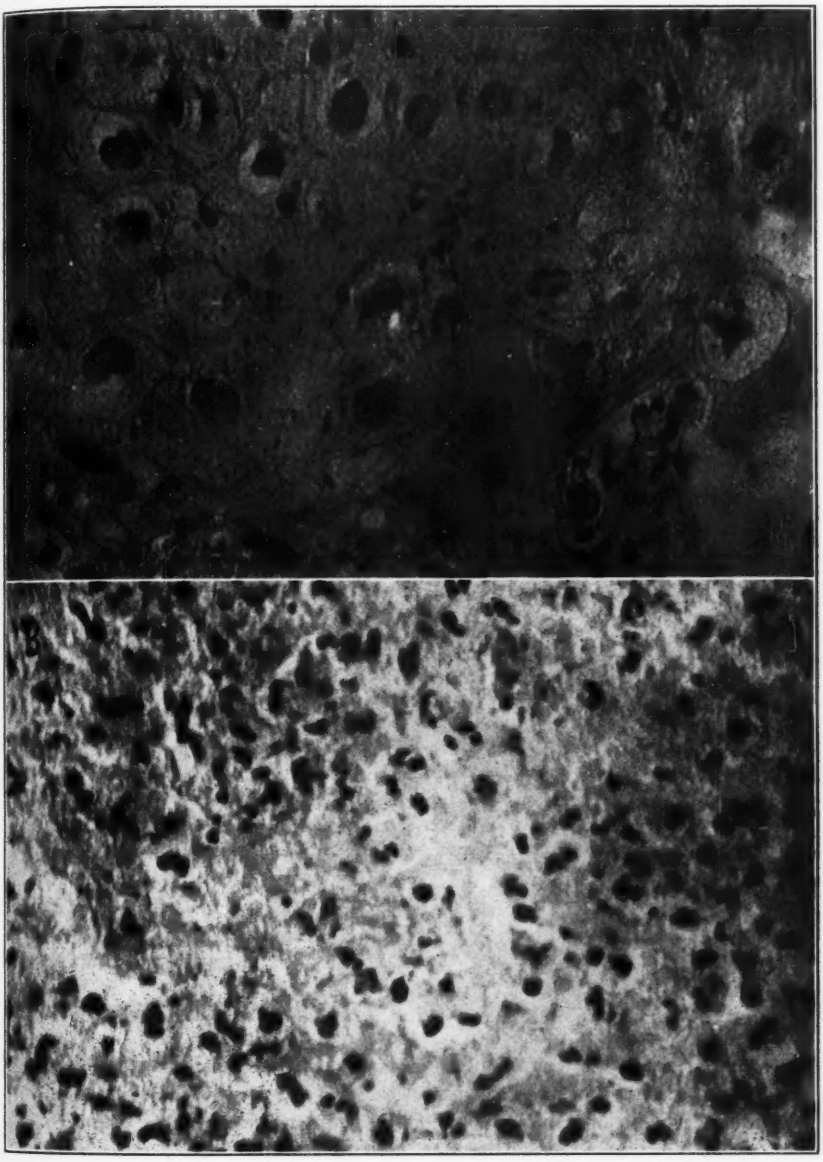

Fig. 1.—Photomicrographs of a senile keratosis showing characteristic changes following applications of resin of podophyllum (*A*) and late necrotic changes (*B*). Similar changes were found in the other epithelial growths studied.

Sullivan and King found that colchicine and resin of podophyllum produced similar effects in both normal and verrucous epidermis. Briefly, they found thickening of the cell walls, perinuclear vacuolization, large cells with dispersed chromatin granules, pyknotic nuclei, clumped and distorted nuclear remains, all as characteristic changes resulting from the application of resin of podophyllum.

About three years ago we began using repeated applications of 30 per cent resin of podophyllum in mineral oil in the treatment of a few seborrheic keratoses. Encouraged by our results, we treated a patient with

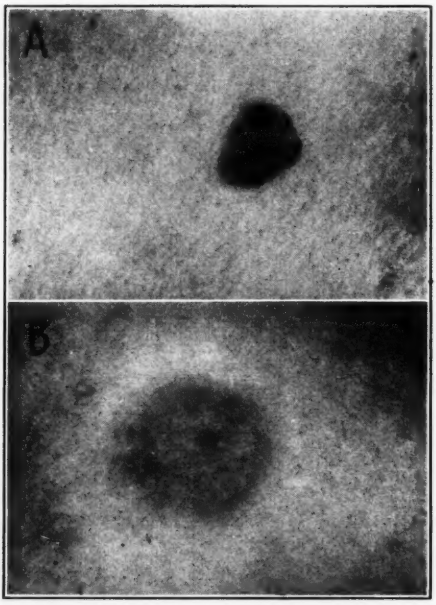


Fig. 2.—Seborrheic keratosis before (*A*) and one month after treatment with resin of podophyllum (*B*).

multiple superficial epitheliomatosis. A good clinical result was obtained, and microscopic studies revealed changes similar to those observed in condyloma, although occurring only after more prolonged application than is necessary in the latter. More recently we treated a series of persons with basal cell epithelioma, both of the multiple superficial and the infiltrating types, and seborrheic, actinic and roentgen ray keratoses. Although the longest periods of post-treatment observations had been a little less than a year at the time of writing and in some cases we were unable to follow the course for more than a few weeks, the results had been so good that we felt justified in making a preliminary report.

METHOD

In the first cases we rimmed the lesion with a zinc and starch paste to protect as much of the normal skin as possible, applied 30 per cent resin of podophyllum in mineral oil and followed the application with an occlusive dressing to promote maceration and facilitate action of the resin of podophyllum. This dressing was

Fig. 3.—Basal cell epithelioma before (*A*) and six months after treatment with resin of podophyllum (*B*).

changed every two or three days, necrotic tissue being removed and fresh resin of podophyllum being applied. Later we began using 20 per cent resin of podophyllum in compound tincture of benzoin. Marks [6] suggested the use of 15 per cent of the

6. Marks, M. M.: Condyloma Acuminata, J. Missouri M. A. **44**:749 (Oct.) 1947.

drug in this vehicle for the treatment of condyloma acuminata. This preparation more nearly confines the action of the resin of podophyllum to the area of application. We have found that daily applications of this substance, which is allowed to dry and then covered with gauze, form the most satisfactory method. Before each reapplication the necrotic slough must be removed by gentle curettage or

Fig. 4.—Large basal cell epithelioma on back of neck before (*A*) and three months after treatment with resin of podophyllum (*B*).

wiped away with gauze. The adjacent skin becomes inflamed and macerated and desquamates, but the action on this normal skin is not deep. The growth rapidly sloughs out in successive layers, and one can easily determine the border between normal tissue and the thicker and deeper epithelial growth. Patients are warned to be extremely careful not to tamper with the dressing for fear of transferring

minute quantities of resin of podophyllum to the eyes. In a few cases of multiple lesions, situated away from the face, and in cooperative patients, the dressing has been omitted.

## RESULTS

Our experience established to our satisfaction that resin of podophyllum applied sufficiently and with due attention to removal of necrotic material as it becomes evident has a lethal effect on epithelial tissue in the types of lesions we are reporting. It seems to be not so much a matter of what proportion of these lesions will respond to treatment as of how thorough the treatment has been. Recurrence is evidence that treatment was not sufficient to reach all the epithelial cells involved. We wish again to emphasize the necessity of thoroughly removing all necrotic tissue at each dressing before reapplying the resin of podophyllum. Pertinent data concerning treatment are presented here in

*Epitheliomas and Keratoses Successfully Treated with Resin of Podophyllum*

| | No. of Cases | No. of Lesions | Average Length of Treatment, Days | Healing Time, Days | Average Length of Post-Treatment Observation, Months |
|---|---|---|---|---|---|
| Multiple superficial basal cell epithelioma | 2 | 45 | 12 | 10 | 7 |
| Small infiltrating basal cell epithelioma | 11 | 11 | 9 | 7 | 6.5 |
| Large infiltrating basal cell epithelioma | 2 | 2 | 15 | 14 | 2.5 |
| Senile and actinic (solar) keratoses | 9 | 72 | 10 | 10 | 2.3 |
| Seborrheic keratoses | 7 | 89 | 14 | 10 | 4 |
| Roentgen ray keratoses | 2 | 2 | 8 | 21 | 4 |

tabular form. The results in all reported cases were considered excellent so far as our periods of observation allowed us to judge.

## MICROSCOPIC STUDIES

Studies were made of biopsy sections taken at various stages of treatment of basal cell epitheliomas and the keratoses. The general pattern of cell death was essentially the same for all. Early changes were vacuolization about the pyknotic nuclei and the presence of some swollen cells showing nuclear disintegration, the so-called "podophyllin cells" of Sullivan and King. Later changes, observed in the necrotic sloughs following several days of treatment, may be described as the moderately advanced and the final stages. The areas of the moderately advanced stage still show some "podophyllin cells," but most cells are decidedly swollen, the nuclei are faint or have disappeared, the cytoplasm is either homogeneous or granular and the cell walls are thickened and give an appearance of reticulation. The final stage or complete death of the epithelial cells is represented by a necrotic mass without cell outlines, throughout which are polymorphonuclear leukocytes and degenerated nuclear remains. In basal cell epithelioma the swelling of the cells and

thickening of the walls is not as pronounced as in the keratoses, but the final picture is the same in all.

## COMMENT

We are presenting a new approach to the treatment of basal cell epithelioma and the various types of preepitheliomatous keratoses. We do not consider this a method of treatment to supersede the more conventional methods. It is a practical method which can be used in many cases, is comparatively simple in application and is relatively free of danger with the exception of the danger of damage to the eye. Rosner [7] called attention to corneal damage from resin of podophyllum applied to verrucae about the eyes, and every precaution must be taken to prevent even traces of the drug from coming in contact with the eyes. Although the treatment is simple, judgment and experience are necessary in the selection of cases just as they are with other methods of treatment, and a knowledge of cutaneous lesions of cancerous and precancerous character is a requisite for any physician who expects to treat them by this as by any other method. There is evidence that early squamous cell epithelioma would respond to this treatment, but it is our opinion that such lesions should have the advantage of irradiation, surgical treatment or electrocoagulation or a combination of these. Healing is quite rapid after treatment with resin of podophyllum, some stimulation of granulation being apparent. Even in cases with radiation damage from previous treatment healing is more rapid than one would expect. Scarring is less than that following electrocoagulation, and the danger of postradiation sequelae is eliminated. It is difficult, particularly in the deeper epitheliomas, to know when treatment is to be stopped, and it is probable that in these lesions destruction of the visible portion of the growth with resin of podophyllum, followed by a moderate amount of radiation, might be preferable to the use of resin of podophyllum alone. This will be a subject for further studies. It is interesting to note that an old drug, resin of podophyllum, has a selective lethal effect on cancerous and precancerous tissues. A search for other drugs with a similar effect, and improvements in technic of application, should follow.

## SUMMARY

A series of cases is reported of basal cell epithelioma and seborrheic, senile, actinic and roentgen ray keratoses successfully treated with resin of podophyllum applied locally. The microscopic changes occurring during treatment are described. Advantages and disadvantages of this method are mentioned.

931 First National Building.

7. Rosner, R. S.: Corneal Insult from Podophyllin, Am. J. Ophth. **29**:1448 (Nov.) 1946.

Dr. H. F. Heslington of El Paso, Texas, and Capt. Francis Jones of William Beaumont General Hospital assisted in studying the histologic sections, and Sgt. Elmer James of William Beaumont General Hospital made the photomicrographs.

## ABSTRACT OF DISCUSSION

Dr. Maurice Sullivan, Baltimore: When it was demonstrated that the cytotoxic effects of resin of podophyllum were similar to those of colchicine, the interest of investigators in the field of cancer research was aroused and trial of resin of podophyllum in the treatment of carcinoma was suggested (King, L. S., and Sullivan, M.: *Science* **104**:244, 1946). Soon after, it was reported that resin of podophyllum produced arrest of mitosis in plant cells (Sullivan, B., and Wechsler, H. I.: *Science* **105**:433, 1947), inactivation of mitotic and meiotic spindles in starfish eggs (Cornman, I.: *Biol. Bull.* **93**:214, 1947) and severe damage to mouse tumor cells in vivo (Belkin, M.: *Federation Proc.* **6** [pt. 2] :308, 1947. Hartwell, J., and Shear, M.: *Cancer Research*, to be published. Ormsbee, Cornman and Berger [5]). A selective damaging effect of resin of podophyllum on mouse tumor cells in tissue culture was demonstrated, and placental serum from a patient previously treated with resin of podophyllum for condylomata acuminata was reported (Ormsbee, Cornman and Berger [5]) to have caused severe damage to mouse tumor cells growing in roller tubes without affecting normal cells growing in the same tubes.

As a prelude to the clinical use of resin of podophyllum for carcinoma my associates and I instituted toxicologic studies (Sullivan, M., and Hilgartner, M.: To be published) to determine whether resin of podophyllum could be used in larger quantities and for longer periods than could colchicine, as the toxic effects of colchicine preclude its use in patients except in small doses. We found that resin of podophyllum is twelve times less toxic than colchicine and its cumulative effect is considerably less than that of colchicine. We have accumulated sufficient data to believe that it is safe topically to apply fairly large quantities of resin of podophyllum over large surface areas without systemic injury to the patient. The symptomatology and pathology of resin of podophyllum poisoning have been studied in animals (Sullivan, M.; Follis, R., and Hilgartner, M.: To be published) to establish familiarity with signs of intolerance to the drug and with a view to ultimate use of the preparation, or the use of one or more of its ingredients, for parenteral or oral treatment. From all present indications the field of usefulness for podophyllin will probably be limited to topical application. However, it is quite possible that new compounds in addition to α-peltatum (Hartwell, J. L.: *J. Am. Chem. Soc.* **69**:218, 1947) will be isolated from resin of podophyllum. Perhaps one of these will exhibit selective tumor-necrotizing properties comparable to resin of podophyllum and have an index of toxicity sufficiently low to permit its administration to patients with metastatic lesions. Of the known ingredients of resin of podophyllum available to me for study picropodophyllin is the least toxic. However, its tumor-destroying property in condyloma acuminatum is nil, and, although it produces some arrest of mitosis in young pigs' skin, such effect is slight in comparison with that of podophyllotoxin, a much more toxic compound capable of destroying condyloma acuminatum (Sullivan, M.; Friedman, M., and Hearin, J. T.: *South. M. J.* **41**:459, 1947). The continued exploration of the properties of all the ingredients of resin of podophyllum is essential to explain the mechanism of the selective action of the resin. McCardell at the National Institute of Health has studied the effects of various compounds and isomers of resin of podophyllum and colchicine, and his observations will be of great importance in consideration of the problem.

I was delighted to hear from Dr. Smith that he had been treating epitheliomas with resin of podophyllum and was ready to make a preliminary statement of his results, as I was eager to compare his clinical findings with ours. Thus far we have treated 18 patients having a total of thirty cutaneous carcinomas (Sullivan, M.; Zell, L., and McCullough, H.: To be published). In 10 patients follow-up has not been complete, as for experimental reasons we have excised sections from the treated lesions in various stages of involution. Of the twenty lesions which were destroyed with multiple applications and permitted to heal, all except one can be considered as showing satisfactory results. In the group of twenty lesions there were twelve small and moderate-sized basal cell carcinomas, six large superficial intraepidermal carcinomas and one massive prickle cell carcinoma. The one treatment failure occurred with the massive basal cell carcinoma. This tumor measured 12 cm. in diameter and was at least 4 cm. thick. After hearing a description of Dr. Smith's technic I am certain that we could have "cured" this massive lesion if we had curetted more thoroughly and used occlusive dressings longer to produce more maceration. In all our cases follow-up has been less than six months, and so it is not possible to be certain about the permanency of the "cures" in the nineteen out of twenty tumors. Dr. Smith's paper is particularly valuable at this time because he has arrived at a definite treatment schedule with which to work. We have tried several treatment schedules varying from two applications within seven days to fifty applications within three months but have not arrived at a satisfactory average at this time. The appropriate therapeutically effective factors of duration of application and amount of drug must be determined by numerous clinical trials and similes based on the effects exhibited by normal human and animal skin treated with resin of podophyllum. The tolerance of normal skin to repeated applications of resin of podophyllum is being studied in human beings and in pigs for determination of the maximum time factors of contact with circumjacent normal skin that will permit restitution to integrity of normal skin after withdrawal of the drug. The sensitizing index of resin of podophyllum is high (Sullivan and King [4]). The crux of the problem, therefore, is the determination of the minimum time factor of topical application sufficient to destroy cutaneous carcinoma permanently without producing hypersensitivity and without causing extensive or irreversible damage to the surrounding normal tissue. As Dr. Smith has pointed out, the action of resin of podophyllum differs from the mechanism of Mohs method, which depends on a nonselective destruction of tissue. There is considerable laboratory data to sustain the contention of the selective action of resin of podophyllum, and one of the most impressive clinical observations in our study has been the selective ulceration of tumor tissue; the borders of basal cell carcinomas are channelized by the drug, and the delineation of ulcerative moats outlining previous sites of tumors is clearcut in contrast to the superficial and reversible signs of injury to surrounding normal skin.

As a point of disagreement with Dr. Smith, we have been unsuccessful in the treatment of seborrheic keratoses with resin of podophyllum. We have also failed in the treatment of various other keratinized tumors and are studying the effects of keratin on podophyllotoxin to determine whether keratin has a counteracting effect on this important ingredient of the resin. It is more likely that the age and type of epidermal cells are the influencing factors on the selective action of resin of podophyllum, as rapidly growing tumor cells, embryonic cells and the epidermal cells of young animals are more susceptible to the action of resin of podophyllum than are the epidermal cells of older, slowly growing tumors and the normal epidermal cells of adult animals and human beings (Sullivan, M., and Hilgartner, M.: To be published).

Dr. A. Fletcher Hall, Santa Monica, Calif.: I certainly enjoyed Dr. Smith's excellent paper, although he "beat me to the draw," so to speak, in reporting his use of resin of podophyllum. About two years ago, I started using resin of podophyllum on my own skin: I had fifteen or more keratoses on my face and have had a couple of epitheliomas, of which I did not make biopsies but believed to be of the early basal cell variety. Subsequently I have treated numerous keratoses of the senile type on others and a few lesions which I believed to be superficial basal cell carcinomas but on which I did not do biopsies. I began by using a 25 per cent solution of resin of podophyllum in alcohol and acetone, equal parts, but more recently have added 20 per cent salicylic acid to this solution in an effort to stop small bleeding points after curettage. I precede application of the solution by light curettage if an aggregation of keratotic scales is present; if not, and a pink, rough, sandpaper-like surface is presented, I paint on the solution without curettage. When the solution dries, a pellicle-like scale forms; after a few hours, the patient may wash his face without danger of his doing so interfering with healing. After about twenty-four hours, the treated area becomes fairly tender and remains so for several days. In a week to ten days or two weeks, the pellicle peels off as a scale leaving a slightly pink area which loses its pinkness within a week or two and leaves no scar. This method is quite valuable in painting bald heads on which there are multiple senile keratoses; in such a condition one may paint the entire top of the head. One application is usually enough, but persistent points may be repainted ten days to two weeks later.

We have also treated cutaneous horns in this manner; the horn portion is plucked off, and a cotton swab saturated with the solution is plunged into the site from which the horn was removed. This site heals, as a rule, after one application, with remarkably little scarring.

There is one other type of lesion in which this solution has been used: multiple lesions of molluscum contagiosum in young children, which it is almost impossible to treat individually with electrocoagulation or with other types of therapy. These lesions can be treated without any discomfort to the child by painting them with the resin of podophyllum solution once a week; within five or six weeks the lesions will have disappeared.

Dr. Marcus R. Caro, Chicago: There is one serious drawback to the use of even selective drugs in local applications in the treatment of cancer of the skin. It is extremely difficult to know just when to stop the applications and to permit the ulcer to begin to heal. Dr. F. E. Mohs introduced a chemosurgical treatment of external cancer in which he makes a careful histologic examination of successive layers of tissue that he removes. Unless one persists until one reaches a carcinoma-free layer there may be some carcinoma cells left behind at the base or there may be a linear track of carcinoma extending laterally. Either situation would lead to a recurrence. I should like to stress the fact that there must be some form of histopathologic control of the tissue that is removed before one can consider any topical application as an effective or safe treatment for cancer of the skin.

Dr. Norman N. Epstein, San Francisco: I should like to emphasize what Dr. Caro has mentioned, that the work of Mohs shows that many carcinomas of the skin have prolongations in different directions beyond their apparent limits. I should like to ask whether resin of podophyllum affects the normal skin of the border of these lesions sufficiently to take in possible prolongations of this sort.

Dr. Samuel Ayres Jr., Los Angeles: I was very much interested in this technic. I should be interested in knowing the degree of local reaction and whether or not pain was an element, such as to require local anesthetics as the treatment progressed.

DR. LESLIE M. SMITH, El Paso, Texas: I am very grateful to Dr. Sullivan and also to the other discussers. As to microscopic examination, on some of the larger lesions we have done three or four biopsies during the course of and after treatment. For large infiltrating lesions biopsy should certainly be done. In some superficial epitheliomas, with some experience one can tell pretty well without a biopsy when cure has been attained. In some superficial lesions, after treatment the only scar we found was that at the site of removal of tissue for biopsy. As to the use of resin of podophyllum around the lesion, I think it should always be applied beyond the visible limits of the growth. It does have a selective action on epitheliomatous tissue, penetrating these tissues and not destroying collagenous tissues. Dr. Ayres asked about pain. With the larger lesions there is some pain. Some patients complained of lack of sleep and of feeling bad after the reaction began. I don't think that is a toxic reaction at all but just a feeling due to the pain and lack of sleep. There are maceration and tenderness and superficial necrosis wherever the resin of podophyllum is applied continuously or repeatedly. There is the danger that a method like this one, which apparently is so simple, may fall into the hands of those not prepared to use it. It should be used only by men properly experienced in the treatment of these growths. I think it is a method that has some promise if applied thoroughly by someone who knows these lesions. It has considerable value in selected cases. Dr. Sullivan has been bolder than I in treating squamous cell growths, but I am sure that early squamous cell lesions can be treated safely by this method. We have treated some cases of senile keratoses in which biopsy showed early malignant changes in squamous cells. These lesions have responded satisfactorily.

# EOSINOPHILIC GRANULOMA

## An Unusual Case with Involvement of the Skin, Lungs and Kidneys

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THE TERM "eosinophilic granuloma" usually refers to a specific bone lesion considered by some (particularly Jaffe and Lichtenstein [1]) to be the early monosymptomatic form of Hand-Schüller-Christian disease. This concept is well supported by Holm, Teilum and Christensen's [2] report of 6 cases showing a gradual transition from the early solitary lesion to the picture of Hand-Schüller-Christian disease.

However the term "eosinophilic granuloma" has not been confined to this entity. It has been applied to other conditions, apparently different from Hand-Schüller-Christian disease. Curtis and Cawley [3] reported the case of a girl whose condition was similar to a seborrheic dermatitis with small, red, discrete and coalescent papules on the buttocks and eroded patches in the mouth. In each axilla weeping, sharply demarcated erythematous papules were noted. Roentgenologic examination showed destructive lesions of a rib and the ilium. Biopsy specimens of the lesions of the skin showed a picture suggestive of reticuloendothelioblastoma with histiocytes and eosinophils.

Kendrick and Woodruff [4] reported the case of a girl 12 weeks of age with swelling in the shoulder and pain on motion of the arm. Roentgenograms demonstrated lesions of the scapula on the same side, as well as of one rib and one vertebra. Biopsy of tissue from the scapula revealed granulation tissue composed of histiocytic cells, masses of eosinophils and occasional patches of lymphocytes. In addition there

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1. Jaffe, H. L., and Lichtenstein, L. M.: Eosinophilic Granuloma of Bone, Arch. Path. **37**:99 (Feb.) 1944.

2. Holm, J. E.; Teilum, G., and Christensen, E.: Eosinophilic Granuloma of Bone—Schüller-Christian's Disease, Acta med. Scandinav. **118**:292, 1944.

3. Curtis, A. D., and Cawley, E. P.: Eosinophilic Granuloma of the Bone with Cutaneous Manifestations: Report of Case, Arch. Dermat. & Syph. **55**:810 (June) 1947.

4. Kendrick, J. I., and Woodruff, J. B., Jr.: Eosinophilic Granuloma: Report of Case with Both Osseous and Cutaneous Lesions, Cleveland Clin. Quart. **15**:26, 1948.

was a slightly scaly, dull red rash over the back, chest and buttocks. Biopsy of a specimen from the skin revealed a dense infiltration of the upper portion of corium of lymphocytes, large mononuclear cells and frequent eosinophils in small patches.

A case of eosinophilic granuloma of the bone with pulmonary involvement was reported by Weinstein, Francis and Sprofkin.[5] Their patient was a 30 year old man with roentgenologic evidence of destruction in the left parietal and occipital bones, ilium, os pubis and one vertebra. In addition there was a fine nodular type of infiltration in the upper half of both pulmonary fields. Biopsy of the bone revealed chiefly histiocytes and large cells with a single irregularly shaped nucleus and pale pink cytoplasm. There were many foci of eosinophils and one or two areas of fairly dense lymphocytic infiltration. There was a decided increase in fibrous connective tissue and capillaries.

The aforementioned cases have all been cases of eosinophilic granulomas of the bone and skin or lung. In the following cases eosinophilic granulomas were found in the skin alone.

Lever[6] reported a case in a woman 47 years of age with a purple lesion on each cheek. These were of ten years' duration and had gradually enlarged. Biopsy showed the epidermis to be of normal thickness and revealed an extensive infiltration of the corium in which eosinophils predominated but neutrophils and histiocytes also were numerous. A few lymphocytes and plasma cells were present throughout the infiltrate. Mast cells were conspicuous. The capillaries and precapillaries were thickened. Lipid found in large foam cells was doubly refractive, containing cholesterol esters.

Cerutti[7] reviewed the literature on eosinophilic granuloma of the skin and found 7 cases reported in the European literature. The first of these was reported by Martinotti[8] and occurred in a young soldier with an ulcer of the leg of several months' duration. The ulceration was deep and had sharp borders. The lesion showed loose connective tissue with fibroblasts, lymphocytes and abundant eosinophils.

The next case, also reported by Martinotti,[8] concerned a man 18 years of age with a diffuse skin eruption of a polymorphous erythema-

5. Weinstein, A.; Francis, H. C., and Sprofkin, B. F.: Eosinophilic Granuloma of Bone: Report of a Case with Multiple Lesions of Bone and Pulmonary Infiltrations, Arch. Int. Med. **79**:176 (Feb.) 1947.

6. Lever, F.: Eosinophilic Granuloma of the Skin: Its Relation to Erythema Elevatum Diutinum and Eosinophilic Granuloma of the Bone; Report of a Case, Arch. Dermat. & Syph. **55**:194 (Feb.) 1947.

7. Cerutti, P.: The Eosinophilic Granuloma, Dermatologica **85**:90, 1942.

8. Martinotti, L.: New Contribution to the Study of Bowen's Disease in Relation to the Other Forms of Superficial Epitheliomatosis of the Skin, Gior. ital. d. mal. ven. **65**:176, 1924; cited by Cerutti.[7]

tous type. Scabs formed, and their detachment led to ulcerations. Two nodules of episcleritis were found to be full of eosinophilic cells. Cryptococcus ruber Demme was isolated from the blood, liquid of the bullae, urine and serous fluid from the right arm. Biopsy specimens taken from the margin of an ulceration and from a nodular lesion showed abundant infiltrations of lymphocytes, fibroblasts, epithelioid cells, plasma cells, polymorphonuclear leukocytes, mast cells and many eosinophils.

Another case of Martinotti's,[8] reviewed by Cerutti,[7] concerned a girl aged 17. The blood picture showed an eosinophil count of 22 per cent. The cutaneous lesions first appeared at the age of 11 at the level of the eyelids and later involved the limbs, being associated with rather intense pruritus. The right lower lid showed a semilunar livid red infiltration covered by smooth epidermis and of firm consistency like a syphiloma. Both arms showed very firm painless nodules with a lichenoid surface; the lower limbs showed similar lesions with verrucosities and a dry, infiltrated, pigmented skin. Histologic examination showed acanthosis, edema, dense infiltration consisting of lymphocytes, many eosinophils, epithelioid cells, giant cells, plasmocytes, mast cells and neutrophilic polymorphonuclear leukocytes.

Pautrier, Glasser and Labourgade[10] reported the case of a man aged 25 who acquired anal lesions interpreted as hemorrhoids and showed a dysenteriform syndrome at the same time. The lesion was elevated and verrucous. Rectal examination revealed extension of the induration for several centimeters along the wall of the rectum. A biopsy specimen of the skin showed monstrous acanthosis without hyperkeratosis; the granular layer was lacking in places, and parakeratotic scabs and coagulated serum covered directly the eroded mucosa. The corium showed extremely dense infiltration consisting of lymphocytes, plasmocytes, small histiocytes and many eosinophils. The rectal biopsy specimen showed a similar picture. The authors expressed the opinion that the dominant character of the affliction is its origin around body orifices, and the descriptive term of "peri-orificial eosinophilic granuloma" was suggested.

A case reported by Lapière[11] was that of an old person with lesions of fifteen years' duration, characterized by sclerotic hypertrophy of the skin and papular and nodular formations. There was diffuse ade-

9. Martinotti, L.: Action of Bismuth Salts in Treatment of Syphilis, Gior. ital. d. mal. ven. **65**:498, 1924; cited by Cerutti.[7]

10. Pautrier, L. M., Glasser, and Labourgade: The Eosinophilic Granuloma, Bull. Acad. de méd. de Roumanie **3**:432, 1938.

11. Lapière, S.: Case of Eosinophilic Granuloma, Bull. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **44**:1479, 1937; cited by Cerutti.[7]

nopathy. The iris, ciliary body and sclera also showed nodules. The eosinophil count was 5 per cent at first and rose to 55 per cent. The patient died from cachexia. Biopsy specimens showed acanthosis and abundant eosinophilic infiltrations, particularly around the vessels. In the lymph glands the follicular structure was replaced by infiltrations of the same kind. Some large cells resembled Sternberg cells somewhat but were not identical with them.

Pasini's case [12] was of a 69 year old woman with a pruriginous plaque of eight years' duration, of firm consistency, bluish red and bulging several millimeters over the surface of the skin. The blood picture showed 41 per cent eosinophils. On microscopic examination the epidermis was seen to be normal. The corium and subcutaneous tissue were infiltrated with lymphocytoid cells and very many eosinophilic cells. There was also a pronounced new formation of small blood vessels, the wall of which was thickened by proliferated endothelium.

Cerutti's own case [7] concerned a 41 year old woman. Nodules appeared first at the forehead and the perioral region and later over most of the body. These consisted of nodular elements of varying sizes up to that of a hazelnut, brownish red and of pasty consistency. The most prominent portion of many lesions was necrotic. Histologic examination of a biopsy specimen revealed the epidermis to be thinned in some and thickened in other places. It showed parakeratosis and cellular infiltrations consisting almost exclusively of eosinophilic granulocytes. The vascular walls were thickened mostly by proliferation of the intima.

Nanta and Gadrat [13] reported the case of a 21 year old man with diffuse swellings of the gingiva extending to the palate. There was also a perianal plaque 10 cm. in diameter. The rectal walls were indurated. Histologic examination of the former lesions showed pronounced acanthosis and hyperkeratosis. The infiltrate was composed of lymphocytes, plasmacytes and small histiocytes with a few granulocytes. There was considerable local eosinophilia.

Most recently Vanek [14] reported 6 cases of gastric submucosal lesions. Histologic elements included basic connective tissue infiltration with eosinophilic leukocytes and lymphocytes, the latter occasionally accumulated in rudimentary lymph follicles, and arterioles and blood and lymph capillaries. The tumor-like tissue was grayish yellow and

12. Pasini, A.: Eosinophilic Granuloma (Proliferative Reticuloendotheliosis), Gior. ital. di dermat. e sif. **81**:1, 1940.

13. Nanta, A., and Gadrat, J.: On a Cutaneous Eosinophilic Granuloma, Bull. Soc. franç. de dermat. et syph. **44**:1470, 1937.

14. Vanek, J.: Gastric Submucosal Granuloma with Eosinophilic Infiltration, Am. J. Path. **25**:397, 1949.

soft. Vanek stated the belief that the lesions might be considered inflammatory with a chronic granulomatous nature, or neoplastic (fibroma) with secondary inflammatory reaction.

This review illustrates why the various attempts to classify the eosinophilic granulomas have so far been unsatisfactory. In most instances no known etiologic factor was established, and in a few cases the implicated agents have been different. Furthermore, the appearance of the lesions has been at such variance that a classification on this basis is also impossible. Whether the various cases reported are different diseases under the name of "eosinophilic granuloma" or whether they were only different phases or forms of a single process is not known. In either event it seemed worth while to report a case of an eosinophilic granuloma of the skin which was associated with similar lesions in the lungs and kidneys, since such a combination apparently has not been previously described. Moreover, this granuloma presents some morphologic features different from those described in our review.

## REPORT OF A CASE

The patient was a 71 year old woman. In April 1947 she was admitted to a hospital because of dyspnea and edema of two months' duration, following a severe infection of the upper respiratory tract. A diagnosis of heart failure was made. Treatment with expectorants, diuretics and digitalis was followed by clinical improvement, and the patient was discharged as cured in June 1947.

She was not seen again until March 1, 1948, when her complaint was a cough. Examination of the chest at this time revealed no abnormality. By March 13, the cough had improved and the patient was referred to a dermatologist because of an eruption of the skin of two months' duration. This had begun on the neck, arms and trunk, later spreading to the breasts and legs. Pruritus was present at times, and the skin presented many red, coin-sized, scaly lesions. The impression was that of an atypical pityriasis rosea. Under treatment these lesions improved somewhat. On March 29 the patient was seen again by the internist because of weakness and anorexia. At this time a blood count was done and showed the following: erythrocyte count, 4,700,000 per cubic millimeter; hemoglobin, 93 per cent; leukocyte count, 10,800; eosinophils, 13 per cent; segmented cells, 71 per cent; stab forms, 1 per cent; juvenile cells, 1 per cent; lymphocytes, 12 per cent, and monocytes, 2 per cent.

On April 6, the patient was seen again, at that time because of blisters on her hands. These were of ten days' duration. The former skin rash had now become thick macules in many places, particularly in the right axilla. One of the blisters was opened, and biopsy was done on it on April 8. The pathologic report described atrophy of the epithelium with some edema of the corium. There was also a tendency toward parakeratosis, and at one place the epithelium was infiltrated by numerous lymphocytes and eosinophils. Numerous eosinophils were also found in the corium. The diagnosis was that of a nonspecific inflammatory reaction, consistent with the clinical impression of pityriasis rosea, pellagra or dermatitis herpetiformis, or of a vesicular dermatitis. The patient was then advised to buy an ultraviolet lamp, and after treatments with this was next seen May 6. By this time she had lost weight and was having difficult breathing. Some of the skin

lesions were dry; others were raw. The heart was irregular in rhythm. She was hospitalized May 8. During her hospital stay her temperature remained normal. Examination of the sputum did not reveal tubercle bacilli on two occasions. Results of other laboratory work were as follows: urea nitrogen, 16 mg. per hundred cubic centimeters; blood sugar, 94 mg. per hundred cubic centimeters, and icteric index, 5.9 units. The erythrocyte count on admission to the hospital at this time was 4,020,000, with a hemoglobin content of 71 per cent. The color index was .88. The Kahn reaction of the blood was negative. The leukocyte count was 6,200, and the differential count revealed 75 per cent segmented leukocytes, 13 per cent lymphocytes and 12 per cent eosinophils.

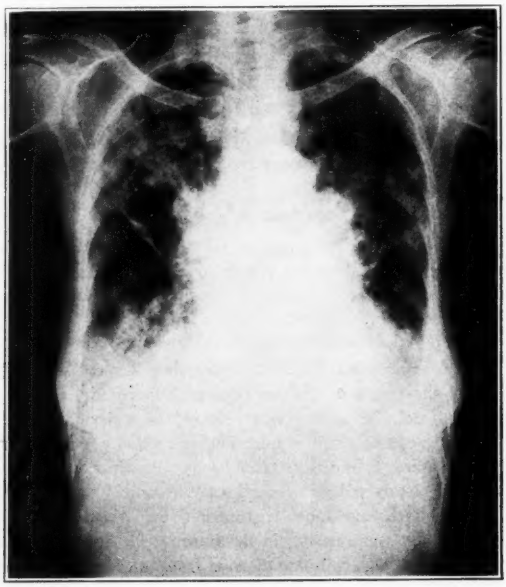

Fig. 1.—Frontal view of the chest, showing enlarged hilar shadows and a radiating mottled form of infiltration of both lungs.

A routine frontal view of the chest on roentgenologic examination showed a very extensive infiltration in both lungs. The hilar shadows were enlarged and their outlines less distinct than usual. There was a radiating linear infiltration in both lungs and also a mottled form of infiltration which was not entirely symmetric. No definite signs of cavitation were seen. In the apex of the right lung and upper lateral axillary area of the same side was a suggestion of local emphysema. The impression was that of extensive bilateral pulmonary abnormality, suggestive of pulmonary vascular congestion associated with a chronic fibrous tuberculosis (fig. 1).

The patient's hospital course was one of rapid progression to her death on May 16, 1948. Permission for autopsy was not obtained until after the body had been removed from the hospital and embalmed.

At autopsy it was noted that the skin of the neck, chest, upper arms and to a lesser extent of the abdomen and thighs was covered with honey-like crusts up to the size of a penny. The crusts were easily removable, leaving behind a slightly elevated grayish red infiltration of the skin. There was no pitting edema.

The upper lobes of both lungs were adherent to the chest wall by old membranous adhesions. On the surface of the lungs as well as within the pulmonary parenchyma numerous nodules were found, some up to the size of a hen's egg. They were rather well defined, and most of them were spherical. The larger foci seemed to have arisen from smaller ones by confluence and showed almost complete necrosis. They appeared on sections opaque and light grayish yellow. The smaller

Fig. 2.—Obliterating panarteritis with necrosis (upper part of the picture). Notice the persistence of certain structures, particularly the blood vessels, in the areas of necrosis (lung).

nodules mostly did not show any necrosis and appeared light grayish white. The appearance of the lesions strikingly resembled the picture in tularemia.

The heart evidenced brown atrophy and moderate coronary atherosclerosis. The kidneys were smaller than normal. The capsule stripped readily. The surface was granular. In each kidney were found a few well defined nodules up to the size of a cherry seed. They were lodged in the cortex immediately beneath the capsule and appeared yellowish white. The only bones examined were a portion of the lumbar spine, the sternum and one rib; the marrow in these appeared grayish red and osteoporosis was present. The skull was not opened.

*Histologic Examination.*—Lung: Microscopically, the lesion in the lung offered a variable picture. It corresponded to that of a granuloma characterized chiefly

by eosinophilic infiltration, severe blood vessel changes and necrosis (fig. 2). There were small foci of granulation tissue more or less well defined, made up of cells similar to fibroblasts; besides some lymphocytes they contained large numbers of eosinophilic cells. Many of these foci showed central necrosis with the structure of the tissue, however, partially preserved. Some of the small granulomas were characterized by extensive karyorrhexis which obscured the cell character. Other foci were particularly large and offered a somewhat different picture from that previously mentioned. Here the alveoli were to a great extent preserved. The wall, however, appeared thickened by lymphocytes, plasma cells, eosinophilic cells and fibroblasts. Many alveoli contained fibrin and erythrocytes, with or without the admixture of lymphocytes, eosinophilic cells and desquamated alveolar epithe-

Fig. 3.—Panarteritis with pronounced thickening of the vessel wall and stenosis of the lumen. In the wall numerous eosinophils are seen (lung).

lium. In some alveoli the eosinophilic cells were very numerous. There were also seen some small abscesses composed of eosinophilic cells only or eosinophilic cells and fibrinous exudate. They might be surrounded by enlarged alveoli filled with eosinophilic cells, fibroblasts, lymphocytes and large mononuclear cells. Foci of fibrosis with anthracosis were also seen in these areas. Some foci were made up of alveoli filled with fibrous tissue as characteristic of carnification secondary to pneumonia. Most striking was the involvement of smaller and larger blood vessels, the walls of which were decidedly thickened by abundantly proliferated cells similar to fibroblasts, often with eosinophilic cells admixed. The lumen, especially of the larger blood vessels, might be greatly constricted by the proliferated intima, frequently containing many eosinophilic cells (fig. 3). The largest foci encountered

were chiefly made up of necrotic tissue which, however, permitted the recognition of certain structures, such as thickened blood vessels, pulmonary alveoli and septums. Thus the necrosis resembled that seen in gumma. Parts of the lung adjacent to the granuloma frequently showed thickening of the alveolar wall by plasma cells, eosinophilic cells, lymphocytes, multinucleated giant cells and many large pale cells, apparently desquamated alveolar epithelium. Within the alveoli, as well as in the interstitial tissue, spindle-shaped empty spaces were seen, surrounded by foreign body giant cells (fig. 4). They represented imprints of foreign bodies evidently lost during the embedding process. Fragments of some, however, were present and appeared to constitute a homogeneous and light gray-stained substance.

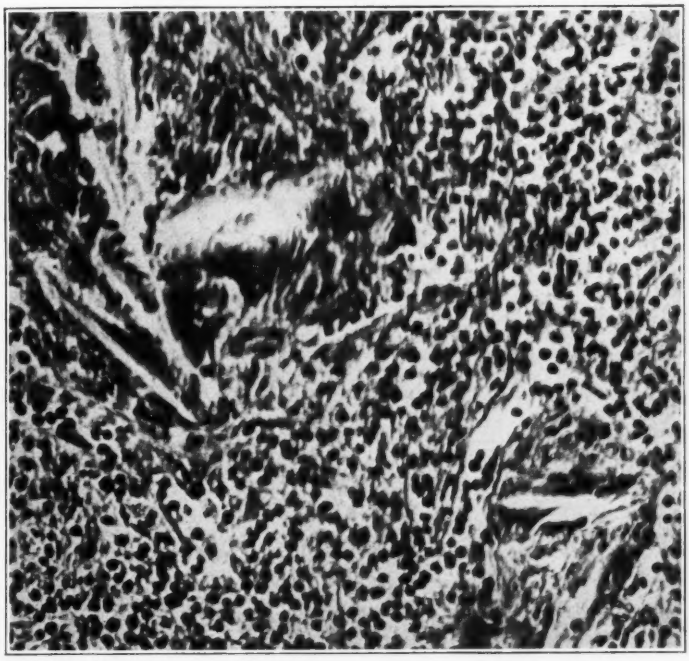

Fig. 4.—Odd crystals within the granuloma surrounded by large foreign body giant cells (lung).

Often enlarged alveoli lined with hypertrophic alveolar epithelium were found within abundantly proliferated stroma made up of fibroblasts and eosinophilic cells. The small bronchi lying within the involved areas showed partial or total replacement by granulation tissue made up of fibroblasts, eosinophils, lymphocytes and a few polymorphonuclear leukocytes. Some sections were stained by the silver impregnation technic of Levaditi and with Gram stain and with methylene blue, but no organisms were seen. Cultures of the tissue were not attempted, as the body had been embalmed.

Skin: The lesion of the skin in some sections was characterized by thickening of the epidermis with proliferation of the papillary body and elongation of the rete

pegs. In many places the epidermis was covered by a scab containing pus cells and broken cell nuclei. The stroma of the pars papillaris of the corium contained a large number of eosinophils, plasma cells and lymphocytes (fig. 5). The pars reticularis contained in some parts only a few small infiltrations composed chiefly of lymphocytes. In other parts, however, the inflammatory infiltration of the pars reticularis of the corium was more pronounced, forming cuffs chiefly of eosinophils around hair follicles and sweat glands. In addition to the inflammatory infiltration there was proliferation of fibroblasts or histiocytes. Here and there ill defined, rather small foci of necrosis with karyorrhexis were seen.

Fig. 5.—Diffuse eosinophilic granuloma of the skin.

Kidney: Sections showed a wedge-shaped, rather large granulomatous focus occupying the cortex and extending down to the pyramids. The renal tissue was entirely replaced either by the granuloma or by glomeruli, and remnants of tubules, more or less well preserved, were still discernible. The granuloma was chiefly made up of eosinophilic cells; however, there was also a small number of histiocytes and lymphocytes. Only a few fibroblasts were seen. There were few ill defined foci of necrosis characterized by pronounced karyorrhexis as described in the comments on the lung (fig. 6). In the neighborhood of the necrosis small hemorrhages were seen. Small arteries within the granuloma were thickened, and their lumen was constricted. Particularly the intima was involved and it, as well as the media, contained many eosinophilic cells.

Liver: It showed the picture of a slight chronic interstitial hepatitis with thickening and lymphocytic infiltration of the portal tracts. Also there was considerable irregular fatty infiltration of the parenchyma, which showed evidence of partial regeneration.

Spleen: The follicles were small and atrophic. They did not contain any germinal centers. The arterioles were thickened and the wall hyalinized. In the red pulp there was a moderate number of plasma cells.

Lymph Nodes: The tracheobronchial lymph nodes were small, anthracotic and indurated. They were not examined microscopically.

Briefly, our case may be described as that of a 71 year old woman who acquired a nonproductive cough and a skin rash, the condition progressing to

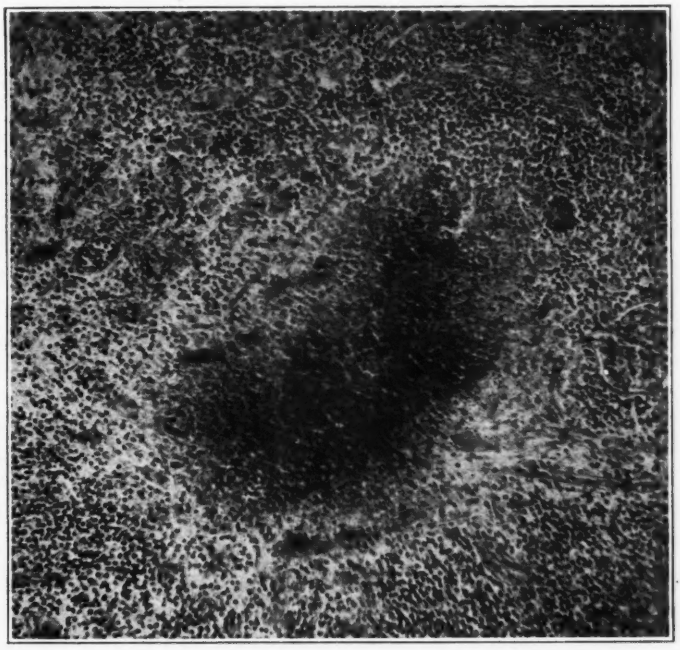

Fig. 6.—Small granuloma of the kidney with central necrosis characterized by pronounced karyorrhexis. The cells in the periphery are chiefly eosinophils.

death in three months. At autopsy a granuloma was found in the skin, lungs and kidneys which was characterized by obliterating arteritis, extensive necrosis and heavy infiltration by eosinophils. No evidence of eosinophilic granuloma was found in the liver, spleen and bones so far as the latter were examined. The tracheobronchial lymph nodes were small, anthracotic and indurated without gross evidence of granuloma.

## COMMENT

With no knowledge of the etiologic factors it is difficult to make a proper classification of this case, as well as of other cases of eosinophilic granulomas which have been reported. First it should be decided

whether a single disease entity is being described under the term. Certainly there is little uniformity of clinical data. The ages of the various patients have ranged from 12 weeks to 71 years. The duration of the lesions has been from ten days to fifteen years. Involvement of bone and skin, of bone and lungs and of skin alone by single or multiple lesions has been reported. With Vanek's and our cases involvement of the gastric submucosa and the skin, lungs and kidneys may be added. Some lesions have been described in the mouth and rectum and in and about the eyes. In some of the cases the condition responded favorably to roentgen therapy; in others it failed to respond, and in 2 it progressed to death. Some patients had normal differential counts of the blood, others had an eosinophil count as high as 50 per cent. With regard to the pathologic picture most of these lesions definitely corresponded to granulomas characterized by the preponderance of eosinophilic cells. Others were described as resembling reticuloendothelioblastoma or submucosal fibroma. A lesion on the cheek contained foam cells laden with cholesterol and its esters. Involvement of blood vessels has been noted in several reports, and necrosis was seen in 2 cases.

The immediate question that arises is whether or not, despite morphologic differences, our case is identical with some of the reported cases or whether it represents a different condition as yet apparently not described. With no information as to the etiology of eosinophilic granuloma only a morphologic classification of these cases is possible. Studies of the morphologic description in cases of eosinophilic granuloma produce the impression that the various pictures described are not all of the same disease. Rather the impression is that one has to deal, at least in some cases, with different pathologic conditions. The comparison of the morphologic picture in our granuloma of the skin with observations described by various authors shows that there are many characteristics in their cases which are absent in our case. A survey of the bibliography shows that in 1 case of eosinophilic granuloma of the skin the epidermis was destroyed and in another case the skin was ulcerated; furthermore, the granuloma was seen chiefly in the deeper layers of the corium and less in the papillary layer, or it was found chiefly in the subcutaneous fat tissue. One author described hypertrophic, partly verrucous vegetations of the skin. As to giant cells, which have been described by some authors, in our case only a few foreign body giant cells, chiefly attached to crystals of an undetermined nature, were seen. Mast cells, foamy cells and lymph follicles with plasma cells, among others, have all been described. None of these changes were seen in our case, which fact suggests that our granuloma may be different from that seen in other cases. This interpretation is supported by the fact that our granuloma, as will be stressed later, shows certain features not mentioned in the cases reviewed in this paper.

No case was found in which a granulomatous lesion was proved in the lungs. The only similar case was one of multiple eosinophilic granulomas of the bones with roentgenologic evidence of an unusual type of pulmonary infiltration. In no case of eosinophilic granuloma of the skin was an identical granuloma described as present in the lungs, at least as far as our search through literature revealed. The same holds true for the granulomatous nodules in the kidneys seen in our case. Morphologically, the process which in the lung strikingly resembled tularemia does not correspond to the picture in any case of eosinophilic granuloma that we could find in the literature.

Many blocks and sections of our case were sent to the Army Institute of Pathology in Washington, D. C., and studied by several members of the Institute staff. No definite diagnosis was made, but "erysipelothrix infection" was suggested as one possibility.

Unfortunately only a portion of the skeleton was examined for lesions in our case, namely, bones of the lumbar portion of the spine, one rib and the sternum. They were free of any granulomatous lesion. It is safe to say that our case has nothing to do with eosinophilic granuloma of the bone and Hand-Schüller-Christian disease, which supposedly are related conditions. Age of our patient (73 years), lack of lipid deposits and absence of foamy cells speak against the identity of the disease in our case with these two conditions. It is particularly the histologic but also the macroscopic picture that makes the granuloma in our case so different from the picture described in other cases. Besides pronounced eosinophilic infiltration there were severe lesions of the vessels in the nature of vasculitis, involving all layers of the vessel wall. There were constriction and obliteration of the lumen, which in turn were responsible for the extensive ischemic necrosis seen in large portions of the lung to an extent like that seen in tuberculosis, gumma, tularemia and other specific granulomas. Grossly, as mentioned before, the lesion closely resembled tularemia. Histologically, the obliterating arteritis and resulting necrosis reminded one of a gumma, with certain structures rather well preserved within the necrosis. The decidedly thickened vessel wall was often so altered that arteries could not be distinguished from veins.

In the skin the proliferative component of the granuloma was less obvious and eosinophilic infiltration prevailed. The microscopic changes in the lungs were of great variety, making the pathogenetic interpretation rather difficult. There were both exudative lesions and proliferative changes of the kind peculiar to tuberculosis. Alveoli filled with eosinophilic cells and fibrin were present, forming a picture similar to the pulmonary change in Loeffler's syndrome. There was also evidence of carnification in some parts as the result of unresolved pneumonia. Most changes were proliferative in nature, as described in the

foregoing remarks. Giant cells were seen but chiefly around odd crystals apparently not previously described as present in cases of eosinophilic granuloma. Scar tissue found in many places indicated the transformation of granulation tissue into scar tissue which is common to all granulomas and indicates a long duration of the process. Actually the pulmonary symptoms could be traced back over a year.

Though the morphologic picture makes it more than probable that the granuloma described in our case is different grossly as well as microscopically from eosinophilic granulomas reported by other authors, it does not shed any light on the etiologic factors. As autopsy was done after the body had been embalmed no attempts were made to obtain cultures from the lesions. Paraffin sections stained by the Gram method, with methylene blue and by the method of Levaditi did not reveal any organisms. The last-mentioned method was also applied by the pathologists of the Army Institute of Pathology, likewise with negative results. Fungi, of which we thought first of all, would have been discovered by these methods in all probability if the granuloma had been due to this type of infection.

The only clues to the possible cause of this granuloma are the changes which the condition showed partially in common with those of periarteritis nodosa. We refer to the arteritis, which by vessel obliteration led to necrosis, and to the eosinophilia. We are, however, conscious of the fundamental differences between the vessel lesions in our case and in periarteritis nodosa. With regard to the possibility of an allergy in our patient, we tried to find reference to the use of drugs, especially the sulfonamides. Our efforts were not successful, as there was no such statement in the history. The eosinophilia of the blood might have been a hint as to a possible allergic nature of the disease, however.

Though our study contributed nothing to knowledge of the etiologic factors concerned in this interesting granuloma, we feel we are entitled to say that the condition may represent an independent etiologic and pathologic entity. The chief purpose of our publication is to direct the attention of other pathologists to similar cases with emphasis on the importance of etiologic studies, such as cultures and animal inoculations, which could not be done in our case because of previous embalming.

RÉSUMÉ

A case of eosinophilic granuloma involving large parts of the skin and lungs and small parts of the kidneys in a female patient 73 years of age is described. The chief characteristics of the granuloma were obliterating arteritis, necrosis and pronounced eosinophilia. This type of eosinophilic granuloma apparently has not been previously described. Its etiology is obscure.

St. Francis Hospital.

# ALLERGIC ECZEMATOUS REACTIONS OF THE NAIL BED DUE TO "UNDER COATS"

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DETROIT

DURING the past eighteen months there have been a number of reports in the literature regarding an unusual nail disorder due to the application of "base coats" or "under coats." In addition, patients with this condition have been presented at various dermatologic meetings throughout the country. The preparations employed are relatively new cosmetics used on nails prior to the application of polish or lacquer and designed to insure greater adherence and to prevent chipping of lacquer. The first of these preparations, "permanail," made its appearance on the West Coast during the latter part of 1946. Because of the early popularity of this preparation, other commercial concerns made available similar or identical preparations such as "everon," "foolpruf," "luron," miraglo,® naylon,® "nailast," "roulac-fixt" and stazon.® Some of the larger and well known beauty shops obtained similar base coat preparations and had them labeled under their own names, informing their clients that the compounds were their own products. There is sufficient accumulated evidence to permit the assumption that all these preparations contained identical or similar ingredients. We were furnished with the ingredients alleged to be present in three of the then commercially available under coats, consisting of two synthetic rubbers and three phenol-formaldehyde resins in a methyl ethyl ketone solvent.

This report is based on data concerning 47 patients who presented unequivocal eczematous reactions of the nail bed seen in our private practices between October 1947 and May 1949.

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Read before the Sixty-Ninth Annual Meeting of the American Dermatological Association, Inc., Hot Springs, Va., May 28, 1949.

From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology, Marion B. Sulzberger, M.D., Director, Post-Graduate Medical School of the New York University–Bellevue Medical Center and the Wayne University Medical College, Department of Dermatology and Syphilology, Loren W. Shaffer, Director.

### CLINICAL FEATURES

All investigators agree on the clinical features, which vary only in degree. In our patients, the condition was limited to the finger nails, where the cosmetic was applied. It did not affect the toe nails, nor did the dermatitis appear elsewhere on the body, as is the case for patients with a sensitivity to nail polish. The clinical features occurring in our patients were as follows:

(1) Discoloration and subungual hemorrhages, varying in color from yellow to red-blue and brown, affecting the distal portion of the nail, associated with small punctate subungual hemorrhages. The hemorrhagic areas appeared to be elongated, with long axes running lengthwise.

(2) Subungual hyperkeratosis of variable degrees, noticeable under the free edge of the nail and extending proximally under the nails.

(3) Onycholysis of varying degrees involving the distal portion of the nails.

(4) Paronychia with edema, erythema and scaling of the finger tips in some instances.

Subjective symptoms of pain, tenderness and paresthesia were reported by some patients. In others, there were no subjective symptoms and the condition was first called to their attention by the manicurist. Two patients in our series (cases 1 and 27) complained of pain of the finger tips within a few hours after the first application and presented pronounced paronychia with pustulation within a few days. This observation would suggest that these patients had already been sensitized by previous exposures, either to bakelite® resins or similar substances, and had a flare-up as a result of the first reexposure to these allergens. In the other patients, symptoms and signs developed in from four to twelve weeks, and longer, after the application of the under coat at one to two week intervals, indicating that these persons had acquired the sensitivity subsequent to its continued use. It is our opinion that the majority of persons fall into this last-mentioned group.

In none of our cases was it necessary to remove the nails for special study, but it has been established that the subungual discoloration was blood pigment, and the material scraped from the under surface of nail clippings gave a positive reaction for blood with the benzidine test. A few patients were examined for the possibility of fungous infection, with negative results.

All our patients were white women, varying in age from 29 to 64 years with an average age of 45 years. We cannot explain why this condition was not observed as frequently in younger persons, unless they were less likely to make use of under coats or unless older patients had

had more time in which to encounter and become sensitized to allergens. For only 9 of our patients was the product self applied, and for the remainder it was applied by the manicurist. In the majority of instances, the first evidence of the disorder was the pigmentation. In some

Experimental case; appearance of nails after four weekly applications of under coats.

instances, the patient read about this condition in the lay press and only then removed the nail polish and observed the condition of her nails for the first time in many months. It was difficult, therefore, accurately to determine the length of time required from the original application of the under coat to the development of noticeable changes in the nails.

As a result of the publicity given to this matter, many women with unrelated changes in the nails (for example, psoriasis, onychomycosis and onycholysis) consulted physicians, even though their condition had been present for several years prior to the use of under coats. We had 25 such patients in our practices. Some of them were needlessly subjected to patch tests and, as anticipated, gave negative reactions. The condition of the nails in these patients did not improve when the use of under coats was discontinued.

TABLE 1.—*Course of Disorders of Nails in Thirty-Two Cases, with Results of Patch Tests*

| Case No. | Age of Patient | Incubation Period | How Condition First Noticed | How Under Coat Applied | Reaction to Patch Tests | Period of Observation | Condition of Nails at Last Examination |
|---|---|---|---|---|---|---|---|
| 1 | 47 | few hr. | Paronychia | Self | Positive | 5 mo. | Decidedly improved |
| 2 | 45 | 3 mo. | Pigmentation | Manicurist | Positive | 15 mo. | Well |
| 3 | 57 | 2 mo. | Pigmentation | Manicurist | Positive | 3 mo. | Decidedly improved |
| 4 | 40 | 5 mo. | Pigmentation | Self | Positive | 3 mo. | Decidedly improved |
| 5 | 57 | 6 mo. | Pigmentation | Self | Positive | 5 mo. | Well |
| 6 | 49 | 2 mo. | Paresthesia | Self | Positive | 5 mo. | Decidedly improved |
| 7 | 57 | 3 mo. | Pigmentation | Manicurist | Positive | 5 mo. | Decidedly improved |
| 8 | 56 | 10 mo. | Paresthesia | Self and manicurist | Positive | 6 mo. | Decidedly improved |
| 9 | 35 | 2 mo. | Pain | Self | Positive | 5 mo. | Well |
| 10 | 53 | 4 mo. | Subungual hyperkeratoses | Manicurist | Positive | 11 mo. | Well |
| 11 | 38 | 8 mo. | Subungual hyperkeratoses | Manicurist | Positive | 11 mo. | Well |
| 12 | 39 | ? | Pigmentation | Manicurist | Positive | 6 wk. | Moderately improved |
| 13 | 47 | ? | Pigmentation | Manicurist | Positive | 3 mo. | Well |
| 14 | 37 | 5 mo. | Pigmentation | Manicurist | Positive | 9 mo. | Well |
| 15 | 29 | 6 mo. | Pigmentation | Manicurist | Positive | 7 mo. | Well |
| 16 | 55 | 3 wk. | Pain | Manicurist | Positive | 3 mo. | Decidedly improved |
| 17 | 64 | 6 wk. | Pigmentation | Manicurist | Positive | 5 mo. | Decidedly improved |
| 18 | 48 | 5 mo. | Pigmentation | Manicurist | Positive | 10 mo. | Well |
| 19 | 50 | 3 mo. | Pigmentation | Self and manicurist | Negative | 7 mo. | Recurrent paronychia |
| 20 | 42 | 1 mo. | Pigmentation | Manicurist | Negative | 6 mo. | Well |
| 21 | 31 | 2 mo. | Pigmentation | Manicurist | Negative | 1 mo. | Slightly improved |
| 22 | 58 | 4 mo. | Pigmentation | Manicurist | Positive | 11 mo. | Decidedly improved |
| 23 | 48 | ? | Pigmentation | Manicurist | Positive | 7 mo. | Well |
| 24 | 41 | 9 mo. | Pigmentation | Self | Positive | 8 mo. | Well |
| 25 | 37 | 11 mo. | Onycholysis | Manicurist | Positive | 5 mo. | Well |
| 26 | 43 | 2 mo. | Pigmentation | Self | Positive | 5 mo. | Decidedly improved |
| 27 | 38 | 12 hr. | Paronychia | Manicurist | Positive | 4 mo. | Well |
| 28 | 36 | 3 mo. | Pigmentation | Manicurist | Positive | 7 mo. | Well |
| 29 | 40 | 9 mo. | Pigmentation | Manicurist | Positive | 9 mo. | Well |
| 30 | 44 | 9 mo. | Onycholysis | Manicurist | Negative | 4 mo. | Well |
| 31 | 52 | ? | Onycholysis | Manicurist | Negative | 4 mo. | Moderately improved |
| 32 | 51 | 2 mo. | Pigmentation | Manicurist | Positive | 9 mo. | Well |

## PATCH TESTS

Thirty-two of the patients in this series were subjected to patch tests with one or more of the various base coat preparations (table 1). One of the commercial concerns furnished us with the methyl ethyl ketone solvent, two synthetic rubbers and three formaldehyde resins contained in their under coat. In addition, we obtained another solution of phenol-formaldehyde resin for patch testing. Patch tests performed on 105 normal subjects and on women with unrelated nail changes all elicited negative reactions. The patch tests were performed in the usual manner, and the patches were permitted to remain in con-

tact with the skin for approximately forty-eight hours. The tested areas were observed at once, thirty minutes later and at weekly intervals thereafter. In tables 2 and 3 are recorded the results of our patch tests.

Sulzberger and associates [1] and Mitchell [2] stated the opinion that this condition is an allergic reaction, whereas Winston and Sutton [3] wrote that they believed "the reaction to be of the sort induced by a

TABLE 2.—*Result of Patch Testing with Various Substances*

| Case No. | Type of Reaction | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Immediate | N | N | N | N | P | P | N | .. | .. | P | .. | .. | .. | .. |
| 2 | Delayed | N | N | N | N | P | P | N | P | P | P | P | P | P | .. |
| 3 | Delayed | N | N | N | N | P | P | P | .. | .. | P | .. | .. | .. | .. |
| 4 | Delayed | N | N | N | N | P | P | N | .. | .. | P | .. | .. | .. | .. |
| 5 | Delayed | N | N | N | N | P | P | P | .. | .. | P | .. | .. | .. | .. |
| 6 | Delayed | N | N | N | N | P | N | N | .. | .. | P | .. | .. | .. | .. |
| 7 | Delayed | N | N | N | N | P | N | N | P | P | P | P | P | P | .. |
| 8 | Immediate | N | N | N | N | P | P | N | P | P | P | P | P | P | .. |
| 9 | Delayed | N | N | N | N | P | P | N | P | P | P | P | P | P | .. |
| 10 | Delayed | N | N | N | N | P | P | N | .. | .. | P | .. | .. | .. | .. |
| 11 | Delayed | N | N | N | N | P | P | N | P | P | P | P | P | P | .. |
| 12 | Delayed | N | N | N | N | P | N | N | .. | .. | P | .. | .. | .. | .. |
| 13 | Delayed | N | N | N | N | P | P | N | P | P | P | .. | .. | .. | .. |
| 14 | Delayed | N | N | N | N | P | P | N | P | P | P | .. | P | P | .. |
| 15 | Immediate | N | N | N | N | P | P | N | P | P | P | P | P | P | .. |
| 16 | Immediate | N | N | N | P | P | P | P | .. | .. | P | .. | .. | .. | .. |
| 17 | Delayed | N | N | N | N | P | P | N | P | P | P | P | P | P | .. |
| 18 | Delayed | N | N | N | N | P | P | .. | P | P | P | P | P | P | .. |
| 19 | Negative | N | N | N | N | N | N | N | N | N | N | N | N | N | .. |
| 20 | Negative | N | N | N | N | N | N | N | .. | .. | N | .. | .. | .. | .. |
| 21 | Negative | N | N | N | N | N | N | N | N | N | N | N | N | N | .. |
| 22 | Delayed | N | N | N | N | P | N | N | .. | .. | P | .. | .. | .. | .. |
| 23 | Delayed | N | N | N | N | N | N | N | P | N | P | .. | .. | .. | P |
| 24 | Delayed | N | N | N | N | N | N | N | P | P | P | .. | .. | .. | P |
| 25 | Delayed | N | N | N | N | N | N | N | N | N | P | .. | .. | .. | P |
| 26 | Immediate | N | N | N | N | P | P | N | P | P | P | .. | .. | .. | P |
| 27 | Immediate | N | N | N | N | P | P | N | P | N | P | .. | .. | .. | P |
| 28 | Immediate | N | N | N | N | N | P | N | .. | .. | .. | .. | .. | .. | .. |
| 29 | Delayed | N | N | N | N | N | N | N | N | P | P | .. | .. | .. | P |
| 30 | Negative | N | N | N | N | N | N | N | N | N | N | .. | .. | .. | N |
| 31 | Negative | N | N | N | N | N | N | N | N | N | N | .. | .. | .. | N |
| 32 | Delayed | N | N | N | N | P | P | N | N | P | P | .. | P | .. | .. |

The substances tested were as follows: 1, methyl ethyl ketone; 2, synthetic rubber; 3, synthetic rubber; 4, phenol-formaldehyde resin; 5, phenol-formaldehyde resin; 6, phenol-formaldehyde resin; 7, phenol-formaldehyde resin; 8, "foolpruf"; 9, "permanail"; 10, "everon"; 11, "miraglo" preparation; 12, "naylon" preparation; 13, "roulac-fixt," and 14, "stazon."

1. Sulzberger, M. B.; Rein, C. R.; Fanburg, S. J.; Wolf, M.; Shair, H. M., and Popkin, G. L.: Allergic Eczematous Reactions of the Nail Bed: Persistent Subungual and Ungual Changes Based on Contact with "Undercoats" Containing Artificial Resins and Rubbers, J. Invest. Dermat. **2**:67 (July) 1948.

2. Mitchell, J. H.: Nail Changes Following the Use of "Base Coats," M. Clin. North America **33**:95 (Jan.) 1949.

3. Winston, B. H., and Sutton, R. L., Jr.: Onycholysis Due to Plastic Adhesive for Nail Lacquer, J. Kansas M. Soc. **49**:37 (Sept.) 1948.

primarily injurious solvent substance rather than an allergen." Sharlit [4] presented his findings in a preliminary publication and in a subsequent report [5] stated that a contact allergen was probably the factor producing these nail changes. Epstein [6] sent questionnaires to all practicing dermatologists in California. One of the questions asked was whether this condition was due to an allergic reaction or whether it was caused by a primary irritant. In the 82 responses, 36 dermatologists had no opinion, 26 stated that they thought the condition was allergic and 20 expressed the opinion that it was due to a primary irritant. There is,

TABLE 3—*Results of Patch Tests with Ingredients and with Under Coats*

| Substance | Reactions | | |
|---|---|---|---|
| | Positive | Negative | Test Not Done |
| 1. Methyl ethyl ketone | 0 | 32 | 0 |
| 2. Synthetic rubber | 0 | 32 | 0 |
| 3. Synthetic rubber | 0 | 32 | 0 |
| 4. Phenol-formaldehyde resin | 1 | 31 | 0 |
| 5. Phenol-formaldehyde resin | 22 | 10 | 0 |
| 6. Phenol-formaldehyde resin | 19 | 13 | 0 |
| 7. Phenol-formaldehyde resin | 3 | 28 | 1 |
| 8. "Foolpruf" | 14 | 7 | 11 |
| 9. "Permanail" | 14 | 7 | 11 |
| 10. "Everon" | 26 | 5 | 1 |
| 11. "Miraglo" preparation | 8 | 2 | 22 |
| 12. "Naylon" preparation | 10 | 2 | 20 |
| 13. "Roulac-Fixt" | 9 | 2 | 21 |
| 14. "Stazon" | 6 | 2 | 24 |

TABLE 4.—*Number of Each Type of Patch Test Reaction*

| Type | Number |
|---|---|
| Negative | 5 |
| Immediate | 7 |
| Delayed | 20 |

therefore, some difference of opinion regarding the mechanism of this disorder. It is our opinion, however, that the condition is due to an acquired allergic hypersensitivity since most of the patients had the first evidence of the condition one to ten months after the beginning of repeated application of the under coat.

Of the 32 patients tested, all but 5 showed eczematous responses to one or more of the test materials. It will be noted that of the 27

4. Sharlit, H., and Fanburg, S. J.: Hyperkeratosis and Onycholysis After Use of New Nail Cosmetic, J. A. M. A. **137**:785 (June 26) 1948.

5. Sharlit, H.: Nail (Hyponychia) Changes Due to Nail Polish Under Coats, to be published.

6. Epstein, E.: Personal communication to the authors.

patients with positive reactions to patch tests, 20 (74 per cent) had responses of the delayed type. In these patients, the tested areas had negative reactions when the patches were removed and had positive ones seven to fourteen days later. In some instances the positive reactions persisted for two months. Seventeen of the patients with positive reactions to patch tests were simultaneously tested with several brands of similar under coats, and all were found to give a positive reaction to one or more of these products.

It is of special interest that none of our patients was found to be sensitive to the synthetic rubbers contained in under coats. Twenty-two of the 27 patch test–positive persons gave positive reactions to ingredient 5, 19 had positive reactions to ingredient 6, 3 reacted positively to ingredient 7, and in only 1 was there a positive response to ingredient 4. All these ingredients were the phenol-formaldehyde resins contained in under coats. Other investigators [7] reported positive reactions to the synthetic rubber. It is evident, however, that in the vast majority of instances the resin is probably the sensitizing factor.

Of the 5 patients with negative reactions to patch tests, 1 (case 19) had had recurrent attacks of paronychia for several years. She acquired the characteristic picture of subungual hyperkeratosis and hemorrhage, with onycholysis, which disappeared in a few months, but she still had recurrent episodes of paronychia at the time of writing. She was retested to the various under coats and the individual ingredients two months after the first patch tests, with negative results. One patient (case 21) had had recurrent attacks of a vesicular dermatitis of the hands, with associated nail changes of many years' duration. She also acquired subungual hyperkeratosis, pigmentation and onycholysis about two months after using an under coat. The condition of the nails had improved slightly when the patient was observed one month after the discontinuance of use of the product.

There were 15 additional patients with the characteristic picture of this condition on whom patch tests were not performed. They were included in this series for the observation of their spontaneous clinical improvement over a period of several months with no type of treatment whatever.

## TREATMENT

The patients were apprized of the nature of this condition so that further exposure to the under coats would be avoided. Wet dressings or compresses with aluminum acetate (Burow's) solution, boric acid or potassium permanganate were advised for those patients with paronychial involvement. Removal of some of the hyperkeratotic material and trim-

7. Sulzberger et al.[1] Sullivan, M.: Subungual Hemorrhages and Hyperkeratoses Due to Everon, Bull. Johns Hopkins Hosp. **84**:11 (Jan.) 1949.

ming of the nails afforded some symptomatic relief. In no instance was it necessary for us to remove the nails. Some patients received fractional doses of roentgen radiation to the affected nails at one to two week intervals. Later, an attempt was made to determine the efficacy of roentgen therapy. Seventeen patients received roentgen radiation to the nails of one hand only and placebo exposure to the nails of the other hand. At the end of the period of observation there was no appreciable difference in the results. In fact, some patients believed that the untreated nails returned to normal more rapidly than did the treated nails. About one third of the patients received no treatment of any kind and seemed to respond as rapidly as did the treated patients. It is our opinion, therefore, that in the majority of instances treatment is not necessary. The patients were permitted to resume the use of nail lacquer, with no untoward results.

The ultimate prognosis of this condition is excellent, since normal nails replaced the affected ones when the application of the under coats was discontinued. The length of time for complete regrowth of normal nails depended on the extent and severity of involvement (three to nine months). One patient (case 1), when seen fifteen months after the onset of her condition, still presented some subungual hyperkeratosis and pigmentation of her thumb nails. This patient had had arthritis of her fingers and associated thickened nails for several years prior to the use of under coats. Another patient had persistent changes in her nails twelve months after the onset. This patient had been under the care of a physician for many years because of pronounced hypothyroidism. She stated that her nails had always been brittle and grew very slowly. It is quite possible, therefore, that the length of time required to regrow normal nails may be increased by unrelated local or general conditions.

## MECHANISM

In the original report by Sulzberger [1] the belief was expressed that the excess of under coat is wiped off at the end of the nail and that in this manner some is forced beneath the nail from the free edge. A simple experiment was devised to corroborate this theory. Two patients were selected who had previously acquired the characteristic nail changes to under coats (cases 2 and 7), and who had positive reactions to patch tests. Prior to the experiment, the nails had returned to normal and the patch tests were repeated with positive results. Four nails of the left hand were used for the experiment; the nails of the right hand served as controls. Two under coat preparations were employed. One was applied to the edge of the nail, the periungual tissues and underneath the distal portion of the nail of the index finger. The same material was applied to the central portion of the nail only, of the third finger, the periungual and subungual areas being carefully avoided.

The procedure was repeated with the second under coat, in a similar manner, to the fourth and fifth fingers, respectively, of the left hand. The materials were applied by us at weekly intervals and then covered in the usual manner with nail lacquer by a manicurist. The first patient (case 2) acquired paronychia of the index and fifth finger after the third application. One week later she presented subungual pigmentation, subungual hemorrhage and onycholysis, limited to the areas where the material had been applied. The second patient (case 7) showed no appreciable changes six weeks after the fifth application. It is our opinion, therefore, that these materials, or parts of them, may dialyze through the nail plate. Experimentally this was proved by Mitchell,[2] who obtained five toe nails from human cadavers and applied one of the under coats to the upper surfaces of these nails. At intervals after application, moistened swabs were used to wipe the under surfaces of the nails. The swabs were washed with water. The washings were collected and were tested qualitatively for phenol. In all instances phenol was detected in the washings within forty-eight hours after application.

## COMMENT

It is of particular interest that the first under coat made its appearance on the West Coast nearly a year before the other brands became available. During that period there were no known cases of an allergic reaction of the nail bed due to the preparation. The distributor of the leading brand of under coat performed a series of patch tests with the finished product and the individual ingredients on 300 women, with no evidence of primary irritation. In addition, the finished product was supplied to 600 women who used the material for six months, as directed, at weekly intervals, without any evidence of untoward reactions. A series of patch tests to determine sensitizing properties was performed by Halpern and Weiss [8] on 200 volunteers, according to the procedure recommended by Schwartz and Peck. There was no evidence of any sensitization, if the "prophetic patch test" can be relied on. Furthermore, the finished product was distributed and used in a controlled community for several months, with no instance of nail changes being reported.

It is estimated that several million women have applied under coat preparations to their nails at one to two week intervals. Information obtained from the leading distributor of this type of under coats indicates that the company had distributed sufficient material for fifty million applications. It was intimated by Gottschalk and Weiss [9] that the

8. Halpern, L., and Weiss, R. S.: Personal communication to the authors.

9. Gottschalk, H. R., and Weiss, R. S.: Studies on Sensitivity to Sulfonamide Ointments, Arch. Dermat. & Syph. **56**:775 (Dec.) 1947.

incidence of epithelial sensitization may depend on the size of the area of application and on whether or not the sensitizer was applied to a previously damaged or inflamed skin. Since the area of application was relatively small, and since the nail beds were probably not previously damaged or inflamed, the incidence of sensitization was probably quite small. This contention is borne out by the fact that relatively few cases of proved allergic reactions to under coats have been reported throughout the United States, when the very large number of women who used this type of nail cosmetic is considered. It is our opinion, therefore, that the under coat preparations are not necessarily highly potent cutaneous sensitizers, as they have been considered by other investigators. They might have become so had they been routinely applied over large areas and, particularly, on diseased or damaged skin.

## CONCLUSIONS

1. Under coats containing synthetic rubbers and phenol-formaldehyde resins are capable of producing unusual allergic nail changes, consisting chiefly of subungual hyperkeratosis, subungual hemorrhage and onycholysis.

2. The principal offending substances, or sensitizers, appear to be the phenol-formaldehyde resins. These may reach the nail bed by being forced under or around the nail. There is evidence that they may dialyze through the nail plate.

3. The prognosis is excellent. The nails return to normal, even without treatment, when the use of the under coats is discontinued.

## ABSTRACT OF DISCUSSION

DR. JAMES H. MITCHELL, Chicago: The first patient with this condition that I saw was referred to me Feb. 12, 1948, by Dr. Maurice Oppenheim, who wished to have a thorough examination for possible onychomycosis. The appearance of the nails was unique in my experience, and I realized at once that I had never seen such a clinical picture before. In an attempt to obtain material for a microscopic and cultural examination, I found the subungual tissue so hard that scraping would not remove it and that nothing short of cutting the tissue would supply material for examination.

Intensive history taking disclosed the fact that the patient had been having applied a preparation new to me called "everon," marketed by Revlon.

Within a few days after I saw the first case, Dr. Bernard Yaffe brought a patient to me for consultation. I saw at once that the patient presented the same clinical picture, and she promptly answered in the affirmative my question of whether she had been having "everon" applied to her nails.

These 2 cases were presented at the monthly meeting of the Chicago Dermatological Society in March 1948. The presentation of these cases resulted in a very lively discussion by the members of the society.

As a result of the presentation of these cases, Mr. Soroko, general manager of the Revlon Company, called on me and offered every possible aid to solving the

problem. He left two solutions, labeled A and B. Patch tests made with these solutions singly and in combination gave negative reactions, whereas patch tests made with "everon" had strongly positive reactions at the time of the presentation of the cases.

Inasmuch as it was intimated that "everon" and similar preparations were condensation products of formaldehyde and phenol, fresh normal skin was placed in "everon" for forty-eight hours for the purpose of sectioning. However, the skin was so hardened that it could not be sectioned. Another attempt was made to cut the tissue after ten hours, but in even that short period of contact there was too much hardening for satisfactory sectioning.

Dr. Marion B. Sulzberger, New York: I admit and acknowledge my error when I previously reported that these substances got in only around and under nails and did not go through the nails. I saw the case in which Dr. Rein applied the substance to circumscribed areas in the center of the nail, carefully avoiding the edges. Only the area just beneath the site of application became affected; ergo, the material actually went through the nail plate. Another point I should like to bring up is one that I apparently mentioned six or seven years ago in discussing a paper on dermatitis in the bakelite® manufacturing industry. I brought out that it was some combination in the phenol-formaldehyde resin which was the common allergen. Neither the phenol alone nor the formaldehdye solution alone was the usual allergen. Here again, I believe this statement holds true. It is the compound and not the separate ingredients which causes the reaction. It seems quite remarkable that some of the resins tested by Dr. Rein were much less likely to elicit reactions than were the others. It would be interesting to find out why some are so much less harmful than others in these patients. Another point I should like to make is that in 2 of the cases we tested there was a reaction to the rubber constituent. In the studies of Dr. Mitchell and Dr. Rein no such cases were found. Of course, it is well known that rubber and compounds in rubber both synthetic and natural do not all too uncommonly produce contact dermatitis. Like Drs. Rein and Rogin my associates and I also found that these cases usually go on to cure when the nail has "grown out."

Dr. Marcus R. Caro, Chicago: I had the privilege of examining the sections from the biopsy specimen of the patch test reaction from 1 of Dr. Mitchell's cases. To me the significant observation was the complete absence of edema or acanthosis in the epidermis accompanied with extreme edema in the upper part of the corium. It is my opinion that the substances under discussion dialyzed through the nail and produced the inflammatory changes in the nail bed in the same way that they passed through the epidermis in the patch test to produce the inflammatory changes in the corium. The absence of inflammatory changes in the epidermis is strong evidence against the suggestion that was made of an epidermal sensitization.

Dr. Herman Sharlit, New York: Rein and Rogin's presentation deals with a unique and now extinct episode in clinical dermatology, and as we sound requiem over it we might with profit recall the lessons it taught us.

First, it gave dermatologists the opportunity to act promptly, vigorously and effectively in defense of the public weal, for it was dermatologists who took the initiative in bringing about the removal of these hurtful products from the market.

Second, it demonstrated that while the hyponychium is modified skin, it too can be damaged by an allergic mechanism. Furthermore, in any attempt to anticipate the production of an allergic state in it, the use of patch testing of the skin is completely futile.

And lastly, the use by Dr. James Mitchell of cadaver nails to demonstrate the probable manner of access of the noxious agent to the hyponychium (application of the modified phenol-formaldehyde resin to one surface of the nail and the demonstration of the presence after a time of phenol on the opposite surface) forcibly called our attention to the availability of such a technic in studies dealing with keratin and the keratinous layer of the skin as a dialyzing membrane.

I most certainly will keep this procedure in mind whenever the occasion arises in studies dealing with absorptions into and through the surface of the skin.

Dr. Richard I. Sutton Jr., Kansas City, Mo.: The authors alleged that the nail bed reaction was allergic and eczematous, while they recognized that the patients were subjectively asymptomatic. I have not hitherto observed an allergic eczematous reaction which did not itch, burn and call attention to itself in the mind of the patient. Reactors to patch tests who had an eczematous condition—and that was not always the case, for some persons with the changes in the nail bed did not show allergic patch test reactions—were, I will guess, quite conscious of the symptoms the positive reactions produced. Thus the patch test did not reproduce the disease. When Winston and I reported our cases, we thought we were observing the influence of a solvent which penetrates the nail and provokes something analogous to a foreign body reaction in the epithelium of the nail plate. Such a phenomenon would be classed as being due to primary injurants rather than allergens.

Dr. H. J. Templeton, Oakland, Calif.: In view of the fact that these nail lacquer bases may liberate phenol or a phenol compound from phenol-formaldehyde resins, it occurred to me that the damage to the nail bed might be analogous to the gangrene which was occasionally seen in the days of Listerian surgery when phenol was used as a wet dressing on a digit.

Dr. Charles R. Rein, New York: I wish to thank those who were kind enough to discuss our paper. Unfortunately, time will not permit the answering of all the questions. In our series of 47 patients, 2 acquired severe paronychia which occurred within a few hours after the first application of the under coat. Both of these patients had strongly positive reactions to patch tests with the under coat employed. It is our belief that they had been sensitized to a similar or allied substance prior to the first application of the offending base coat. Dr. Mitchell also presented a patient who had positive reactions to patch tests with "lastron." This substance is similar to the usual nail enamels and does not contain synthetic rubbers or phenol-formaldehyde resins. This patient, therefore, had a sensitivity to nail enamel as well as to the under coats.

An important observation is that of the age group of the persons who have the sensitivity to under coats. This would indicate that middle-aged and elderly women are more readily sensitized by the ingredients contained in the under coats. It is our opinion that the nails of such women are more permeable and allow for dialysis of the sensitizing substance. This observation is borne out by the fact that of the 2 sensitized persons selected for the penetration experiment only the older one again acquired the characteristic changes of the nails.

The most important factor at this time is to decide whether the nail changes are due to a primary irritant or to a sensitizing factor. We agree with those investigators who believe that they are due to the latter. This contention is further corroborated by the observations of the largest distributors of one of these under coats.

1. Patch tests on 300 volunteers with the various ingredients contained in under coats and with the finished products gave negative reactions.

2. Six hundred women applied the finished under coats under usual conditions for six months with no evidence of untoward reactions.

3. Spokesmen for this company estimated that it had distributed sufficient material for fifty million applications by 2,000,000 people. On the basis of these figures, the small incidence of untoward reactions favors the theory that the condition represents a sensitization phenomenon rather than response to a primary irritant. If these substances were primary irritants, one would have expected a much higher incidence of untoward reactions.

Although these under coats were voluntarily removed from the American market, some of you may still see persons with these reactions to them, since many "nail cosmetic kits" were sold which contained a bottle of under coat. The purchasers have only recently started to use this material. Furthermore, these under coats are still available in Europe, and some women returning from there may present these nail changes.

From the data presented in our paper and on the basis of the various discussions, it is believed that the unusual reactions of the nail bed are due to a sensitization to some of the ingredients contained in under coats.

# FAVORABLE EFFECT OF HIGH ALTITUDE ON AMERICAN CUTANEOUS LEISHMANIASIS AND LEPROSY

FREDERICK REHM SCHMIDT, M.D.
CHICAGO

IN SOUTH America there are two well recognized types of cutaneous leishmaniasis. Uta, as shown in figure 1, occurs in the high, arid valleys of the Andes at altitudes of 3,000 to 8,000 feet (914 to 2,438 meters). This form of the disease resembles oriental sore, is benign and usually heals within one year with the formation of a scar. The mucous membranes are rarely involved.

On the other hand, mucocutaneous leishmaniasis, or espundia, as it is known in Peru, is found in the moist tropical regions with forests and luxuriant vegetation. One or more ulcers, which usually heal in time, may occur on the legs or arms. Twenty per cent of the patients later acquire ulcerating and mutilating lesions in the mouth and nose. Figure 2 shows a rare disseminated form of the disease. Involvement of the ears produces the characteristic mutilation known as "chicle sapper's ears."

It has long been recognized that neither oriental sore nor uta, when introduced into certain localities, shows a tendency to spread among the population or in the person with the disease.

Mucocutaneous leishmaniasis apparently acts in the same manner, for figure 3 shows a man with the disease who was transported from his home in the hot, humid lowlands to La Paz, Bolivia, which is at an altitude of 11,000 feet (3,353 meters). The ulcer rapidly healed with a minimum amount of treatment with antimony potassium tartrate (fig. 4).

Patients with the lepromatous form of leprosy who are transported from the lowlands to La Paz exhibit a similar although slower regression of the disease.

These observations are in accord with those made in India and China by Strong,[1] who stated that leishmaniasis is confined to the

From the Department of Dermatology, Northwestern University, Edward A. Oliver, M.D., chairman.

Read at the Sixty-Ninth Annual Meeting of the American Dermatological Association, Inc., at Hot Springs, Va., May 27, 1949.

1. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed. 7, Philadelphia, The Blakiston Company, 1944.

low-lying alluvial plains, usually below an elevation of 600 feet (183 meters) and is not observed at all above that of 2,000 feet (610 meters) above sea level. In Italy the disease appears to occur only at low altitudes. The influence of such climatic factors as temperature, humidity and rainfall does not appear to be conclusive.

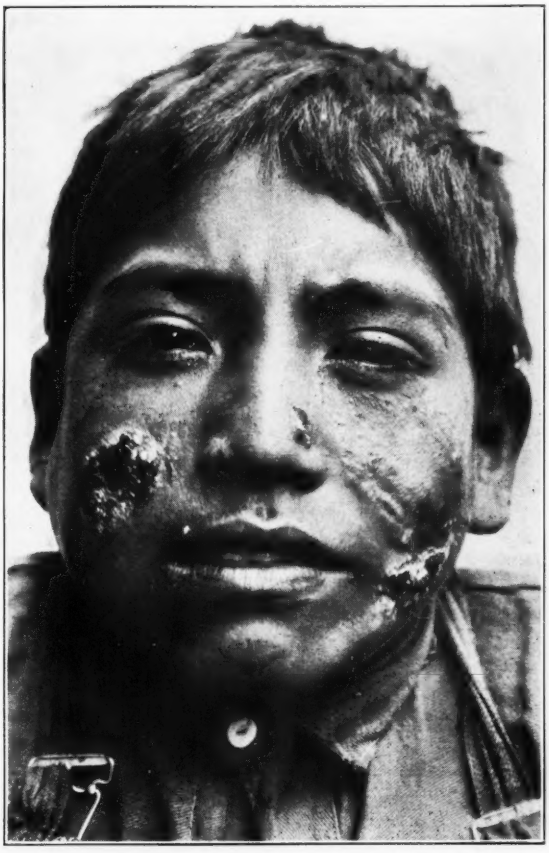

Fig. 1.—A 15 year old Peruvian boy with uta. Note the absence of lesions on the mucous membranes. (Courtesy of Dr. Howard Fox.)

Thus at low altitudes with a hot, humid climate Leishmania and Mycobacterium leprae apparently produce severe visceral and cutaneous symptoms, but at high elevations the diseases caused by these organisms run a decidedly milder course.

The explanation for this difference lies, in my opinion, not so much in the reaction of the tissues of the patient (invaded host) to high altitude, but in the altered biochemical status of the invading parasite. Soule and McKinley [2] studied the influence of varying amounts of carbon dioxide and oxygen on the growth of Myco. leprae. They found that the organism developed optimally when the atmosphere surround-

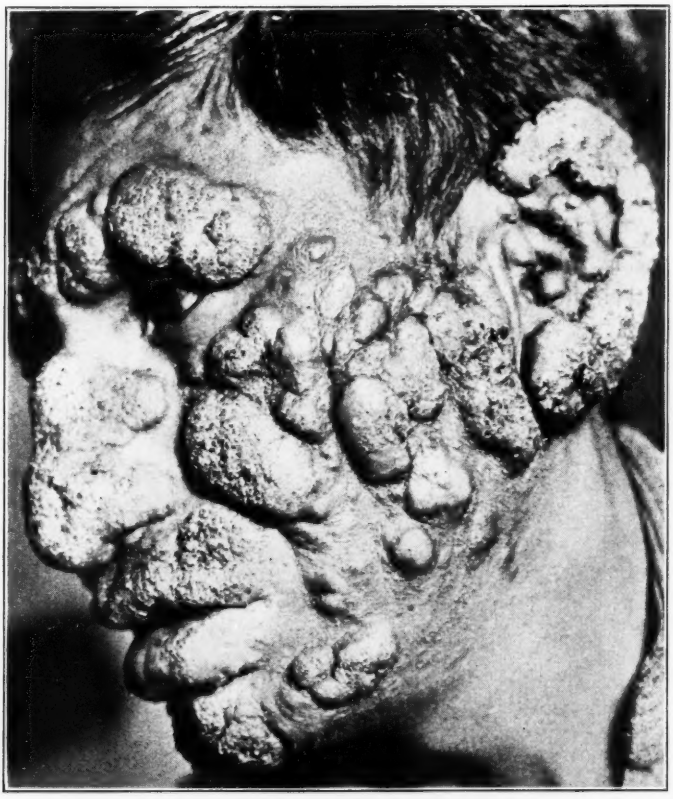

Fig. 2.—Man with primary mucocutaneous leishmaniasis observed in Bolivia. (Courtesy of Dr. L. Prado Barrientos.)

ing the culture contained 10 per cent of carbon dioxide and 40 per cent of oxygen. When the oxygen content was reduced to 20 per

2. Soule, M. H., and McKinley, E. B.: Further Studies on Experimental Leprosy and Cultivation of M. Leprae, Am. J. Trop. Med. **12**:441, 1932; Internat. J. Leprosy **1**:53, 1933.

cent, conditions for the development of the bacillus were much less favorable. The organism lost its ability to reproduce as well as its acid fastness. Atypical forms were found. The experiments of Grau Triana, de Castro Palomino and Conde Mateo [3] appear to corroborate these findings. These authors added oxidase enzymes to the cultures of Myco. leprae, and afterward the organism rapidly multiplied and became acid fast.

Thus oxygen is important in the life and development of Myco. leprae. Grau Triana [4] found that cultures of Myco. leprae are sterilized by heating, which observation appears to indicate that the organism requires certain enzymes that are destroyed by heat. The enzymes

Fig. 3.—Nasal ulceration in a man with metastatic mucocutaneous leishmaniasis who was transported from the lowlands to La Paz, Bolivia, which is at an altitude of 11,000 feet (3,353 M.). (Courtesy of Dr. Victor Villarejos.)

that are necessary to the vitality of man as well as to bacteria in the process of respiration are included in the system of dehydrogenase–cytochrome oxidase enzymes. It so happens that certain bacteria are deficient in these enzymes and, although they carry on the process of respiration, they do so precariously. Myco. leprae is such an organism. It is deficient in cytochrome oxidase.

3. Grau Triana, J.; de Castro Palomino, J., and Conde Mateo, E.: Polymorphic Forms of M. Leprae, Rev. leprol., dermat. y sif. **1**:236, 1944.

4. Grau Triana, J.: Technic for Cultivation of M. Leprae, Rev. leprol., dermat. y sif. **1**:230, 1944.

When Myco. leprae is exposed to a lowered oxygen tension of the blood in a person living at a high altitude, its weak enzyme system cannot cope with the unfavorable environment. The organism loses its vitality and its ability to reproduce in the tissues, just as it does on cultivation in an atmosphere deficient in oxygen. The disease is arrested because the invading parasite has been weakened.

The blood of persons infected with Leishmania shows pronounced biochemical changes. Among the more important ones is the status of

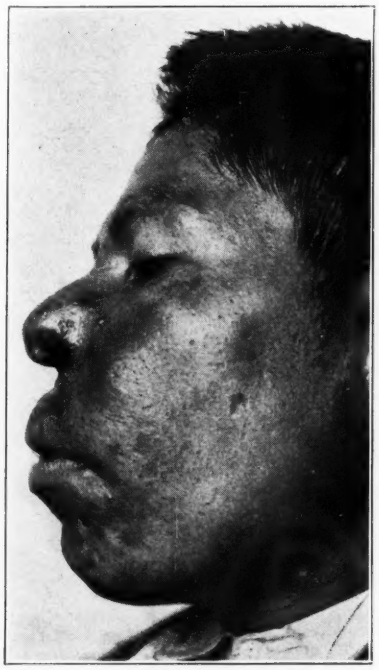

Fig. 4.—The ulcer that was shown in figure 3 healed in a short time in La Paz, Bolivia. Only a small amount of antimony potassium tartrate was administered. There was no further progress of the disease. (Courtesy of Dr. Victor Villarejos.)

the hydrogen ion concentration of the blood. Napier [5] pointed out that its stability in leishmaniasis is easily upset. Petersen [6] showed that a deficiency of oxygen in the tissues leads to a lowering of the $p_H$. Thus a person with leishmaniasis readily responds to oxygen deficiency at a

5. Napier, L. E., cited by Strong.[1]

6. Petersen, W. F.: Man—Weather—Sun, Springfield, Ill., Charles C Thomas, Publisher, 1947.

high altitude with increased acidity of the tissues. His acid-base equilibrium has become labile. This increased acidity is inimical to the vitality of invading organisms. It appears plausible that a person with leishmaniasis has improvement in his condition in localities situated at high elevations above sea level because the invading Leishmania does not thrive in tissues characterized by a lowered oxygen tension, an increased tendency to reduction and an increased acidity.

Investigations [7] carried out on the supply of oxygen to the skin seemed to demonstrate that certain regions are relatively deficient in this element, or, to state it conversely, that there is a greater demand

Fig. 5.—Lepromatous form of leprosy. Note the absence of lesions in the inguinal triangles. (Courtesy of Dr. Guillermo Basombrio.)

for oxygen in these areas. These experiments [7] were carried out in two ways. First, microscopic studies were made of fresh, frozen sections stained with reduced methylene blue and potassium permanganate. Secondly, intradermal injections of methylene blue were made in various areas of the skin. The genitocrural triangles appear to be one of the localities characterized by a deficient supply of oxygen. Figure 5 shows a patient with the lepromatous form of leprosy who has no lesions in the genitocrural folds. The same condition seems to prevail in pinta

7. Schmidt, F. R.: Blood and Oxygen Supply of the Skin, Arch. Dermat. & Syph. **32**:576 (Oct.) 1935.

(fig. 6), where these areas are not achromic. These observations are in agreement with those of Fernández,[8] who found that methylene blue which he had injected into the skin had been reduced to a colorless substance in the same areas. Apparently Myco. leprae does not thrive in these regions because, as a strict aerobe, it does not find enough free oxygen.

The demonstration of lessened acidity on the surface of the skin in the genitocrural folds by Guillot [9] in no way militates against the exist-

Fig. 6.—Pinta. Note the absence of achromia in the cutaneous folds. (Courtesy of Dr. Pedro Weiss.)

ence of acid values under the epidermis. Furthermore, in the mountains there are frequent changes in the barometric pressure that increase the acidity of the tissues.

8. Fernández, J. M. M.: On the Use of Methylene Blue in Dermatology, Rev. argent. dermatosif. **20**:434, 1936.

9. Guillot, C. F.: The $p_H$ of the Skin, Buenos Aires, Argentina, El Ateneo, 1949.

## COMMENT

One may conclude from these clinical and experimental observations that Myco. leprae is a strict aerobe requiring a constant supply of free oxygen. A similar conclusion may be conjectured from the observation of the beneficial effect of high altitude on patients with cutaneous leishmaniasis. Studies of the blood of these patients show pronounced biochemical changes,[5] which include increased acidity of the tissues, which has been easily induced by a deficiency of oxygen.

The idea of lowering the oxygen tension of the blood, thus reducing the amount of oxygen available to the invading parasite, grew out of these studies. An attempt is being made to mimic the effects of high altitude on the patient.

Several approaches to the problem are possible. Fernández [10] reported good results following the treatment of patients with leprosy with unpurified sodium formaldehyde sulfoxylate and ascorbic acid, both of which are reducing substances. Sodium formaldehyde sulfoxylate, also known by the trade name of "rongalite," is part of the molecule of diasone® (disodium formaldehyde sulfoxylate diaminodiphenylsulfone). Investigators at Carville, La., were not impressed with this modality of treatment. Reducing substances such as pro-vitamin K and vitamin E may be used. Secondly, sodium nitrite may be administered to effect a partial conversion of hemoglobin to methemoglobin, possibly by means of high doses of acetanilid.

Experiments are now being made with administrations of cobalt to produce polycythemia in simulation of the increased red blood cell count occurring at high altitudes. Vitamins possessing reducing ability such as vitamin C and folic acid may be combined with a catalyzing mineral like copper. Minerals like copper and cobalt appear to regulate the dehydrogenase and cytochrome oxidase system of enzymes. They may be given by mouth and are free from toxic effects. In addition, patients should be fed large amounts of nourishing food and be instructed to rest a good deal. Small doses of insulin and calcium are indicated because Napier [5] found that the calcium content of the blood is reduced in leishmaniasis. Such a regimen promotes tissue rest and decreases oxidation so that a physicochemical environment is created that is unfavorable to Myco. leprae and Leishmania.

## SUMMARY

Observations in Bolivia and Peru suggest that persons with leishmaniasis and leprosy have a favorable reaction, at least at first, to the climate of localities situated at elevations of 10,000 feet (3,048 meters) and more above the sea.

10. Fernández, J. M. M., and Bergel, M. A.: Treatment of Leprosy Based on the Mechanism of Bio-Oxidation, Rev. argent. dermatosif. **31**:513, 1947.

As this is a preliminary report, a type of treatment is merely suggested whereby the favorable effect of high altitude may be artificially reproduced in patients with these diseases.

The basis for such a treatment rests on the production of a lowered oxygen tension of the blood. This physicochemical status appears to be inimical to the vitality of Leishmania and Myco. leprae.

122 South Michigan Avenue (3).

Dr. Howard Fox, Dr. L. Prado Barrientos, Dr. Victor Villarejos, Dr. Guillermo Basombrio and Dr. Pedro Weiss permitted study of their cases and furnished the photographs of patients included in this article.

## ABSTRACT OF DISCUSSION

Dr. Martin T. Van Studdiford, New Orleans: Our experience with sodium formaldehyde sulfoxylate at Carville, although limited to a very small number of patients with lepromatous leprosy, led us to believe that this preparation was inferior to diasone® or any other sulfone, which, of course, contains the diaminodiphenylsulfone radical. The dose was 5 Gm. administered intravenously daily (maximum) over a period of six to eight months. There occurred a very slow partial resolution of lesions manifested by a slight decrease in the diffuse infiltrations (hardly perceptible in some patients) and some decrease in the size of nodules, which lost some of their turgidity and presented some wrinkling of the overlying skin. There was no change in the number of bacteria found in the scrapings of the skin. The improvement occurred so gradually and slowly that it was difficult to say whether the improvement was due to spontaneous resolution or whether it was due to some antileprotic property in the drug itself. It was necessary to discontinue use of the drug in all the patients treated because of the occurrence of thrombophlebitis of the veins at the site of injection, which condition spread extensively along the course of the veins. The strength of the solution was decreased to 10 per cent from a 20 per cent solution, but the same difficulty occurred in patients treated with the weaker solution. Pruritus and dermatitis were frequent complications.

It would appear from our experience that diasone® contains in addition to the reducing substance sodium formaldehyde sulfoxylate a more potent antileprotic agent. This, of course, must be diaminodiphenylsulfone, the only other radical found in diasone.® The fact that other sulfones—promin® (sodium p,p′ diaminodiphenylsulfone-N,N′-didextrose sulfonate), "sulphetrone" (tetrasodiumphenylpropylamino–diphenyl sulfone tetrasulfonate), promizole® (4,2′-diaminodiphenyl-5′-thiazolylsulfone) and promacetin® (sodium 4,4′-diaminodiphenylsulfone-2 acetylsulfonamide)—all are effective agents against leprosy and all contain in common the diaminodiphenylsulfone group but do not contain as effective reducing agents as sodium formaldehyde sulfoxylate points to diaminodiphenylsulfone as the most effective antileprotic substance in these drugs.

As to the exact mechanism of the action of diaminodiphenylsulfone in vivo on lesions of leprosy, one can do little but speculate. Histologic sections removed after treatment of leprous lesions with a sulfone gives us some indication, however. Lesions about the blood vessels are the first to recede. This observation indicates that there is at least a partial sterilization of the blood stream, with the prevention of the formation of new lesions, allowing the body defense mechanism greater power

to cope with the old lesions, which recede much as in spontaneous recovery. There is thus an indication that the sulfones are bacteriostatic or bactericidal agents against Myco. leprae as they are against Mycobacterium tuberculosis in vitro.

Dr. Schmidt's assertion as to the possible action of diasone® on leprous lesions as due to the reducing substance sodium formaldehyde sulfoxylate, with a lowering of the oxygen tension, is interesting and plausible. It is felt that, in part, improvement in leprous lesions might be due to this phenomenon, but I am inclined to be of the opinion that this is not the main deterrent or influence which causes the improvement observed following treatment with sulfones. Dr. Schmidt's work is in line with that reported by investigators who are working with tissue cultures. It has been found in tissue cultures that if the carbon dioxide tension is increased, fixed tissue cells (macrophages, histiocytes and fibroblasts) are stimulated toward greater phagocytic activity. It may be that the results explained by Dr. Schmidt are not so much due to the reduction in the oxygen tension per se as to the resultant increase in the carbon dioxide tension within the tissues when the oxygen tension is decreased. We have in mind at Carville to conduct some experiments to see what will happen locally to leprous lesions if the skin is in some way mechanically prevented from giving off carbon dioxide. It is known that normally the skin is continuously giving off fairly large amounts of carbon dioxide. Increasing the carbon dioxide tension in the skin presumably would result in greater phagocytosis of Myco. leprae by the fixed tissue cells.

I am curious to know about the eventual results for the patients with lepromatous leprosy who are transported from the lowlands to the high altitudes around La Paz, Bolivia. Do they continue to show improvement, or do they reach a stationary condition after an initial improvement? And might there finally not be a return of leprous lesions even at these high altitudes? It would seem to me that after the tissue cells adjust themselves to the changes in carbon dioxide and oxygen tension that Myco. leprae would again become active and the condition of the patient would become worse again. This question has an important bearing on the much-talked-of climatic treatment for leprosy. As far as the development of the disease is concerned, possibly at high altitudes it is difficult for a person to acquire leprosy. But, after the disease is acquired in another locality, what eventually will happen to it if those who have it are transported to high altitudes? In other words, have any of these patients been followed long enough (say, five or ten years) for it to be known what eventually happens? Initial improvement (say, in the first year or so) does not mean much in a disease as chronic as leprosy.

Dr. Charles C. Dennie, Kansas City, Mo.: I have been very fortunate in several instances in being able to visit the regions in which American leishmaniasis occurs. While I was visiting in Rio de Janeiro the professor of dermatology of the medical school asked us to come out to his clinic. He was presenting a few cases of mucocutaneous leishmaniasis. One of the patients was a short, broad person whose face had a cauliflower appearance, with blue eyes set back deep in his face. The growth was covered with an exudate which had the appearance of French dressing. The professor stated that this was an extreme case of leishmaniasis and that, though the vector was not yet positively known, it was thought that it was the house fly. At this point, a house fly that had been buzzing around the room landed on the patient. From there it flew to the ceiling, looked down at me, dived and landed on my forehead. I made one lunge through the swinging doors to the washroom and scrubbed the area of contact thoroughly. When I returned to the room, the professor, who had observed the entire procedure, said, "You needn't worry, Dr. Dennie; the symptoms of this disease do not appear for at least six months."

Last October a young man came into the office with a peculiar growth on his abdomen which consisted of a ringed lesion about 1 inch (2.5 cm.) long and ¾ inch (2 cm.) wide, with clear skin in the center. He stated that on his first night on the island of Leyte, he had felt an itching and had noticed a little red speck on his abdomen that looked like an insect bite. He scratched the area. The next morning the lesion did not itch, but it never disappeared. It continued to grow over the months. Many forms of treatment were used on it—remedies for ringworm, roentgen radiation, radium and ointments of all kinds—but it continued to grow. It appeared as a red spot, depressed in the center. I asked him if he had any idea what he might have, and he said, "I think I have leprosy." The lesion was the type representative of inoculation lesions. The original lesion was excised entirely. No other signs of leprosy could be found on this man. Three days before I left for this meeting he returned to the office. In the line of excision he had three new lesions. With the use of a local anesthetic these were cut out again. They showed the same pathologic picture. This observation leads me to believe that we have been mistaken in the assumption that there are no organisms of leprosy in the leprous areas.

Histologic examination by Army experts on leprosy revealed histologic patterns typical of leprosy in specimens taken from this patient.

DR. V. PARDO-CASTELLO, Habana, Cuba: It is my understanding that the names uta and espundia are just local names for the same condition. I don't think there is any definite differentiation between the two conditions. This paper gave us a very excellent description of variations of a vell defined condition in different altitudes and climates. A similar situation hold' for pemphigus, which is apparently contagious and a widespread disease requiring special hospitals in Brazil. Then, there is practically no lupus vulgaris in the tropics, but there are all sorts of cases of tuberculosis of the glands, of the lungs or of any other location.

Finally I want to say a word about the treatment of leprosy with the sulfones; it is known that the sulfones, particularly diasone,® are the best preparations for the treatment of leprosy. As for leishmaniasis and its treatment, it is an entirely different condition, not being a bacterial disease.

This paper is interesting and worth a great deal of thought.

DR. MARION B. SULZBERGER, New York: I should like to say a word about some points that Dr. Schmidt's paper brings up. The first of these is the influence of climate on disease. An example is the chronic, infectious disease, lupus vulgaris, which is not exceedingly rare throughout the United States as contrasted with its high incidence in Central European and South American countries and other places. It would also appear that leprosy is for all practical purposes not transmissible in most of the states in the United States but only in the Gulf area. There is to my knowledge not 1 single case proved to have been acquired in New York state. There is therefore just one obsolete law or ordinance regarding lepers in New York city, and that is that patients with "open" leprosy must not be food handlers. However, they may live with their families, marry and circulate. The evidence is strong that leprosy cannot be transmitted in our climate. As far as leishmaniasis is concerned, we are now beginning to see some cases of cutaneous leishmaniasis in New York city with the return of service personnel who served in the Middle East. One important point to be borne in mind is that as leishmaniasis occurs in the United States it tends to take on a chronic form which is in clinical appearance often almost identical with lupus vulgaris. History of a sojourn in an area of endemic leishmaniasis, history of previous ulcerative lesions, the finding of Leishmania, and positive reactions to skin tests make possible a positive diagnosis of leishmaniasis as distinguished from lupus vulgaris.

DR. FREDERICK REHM SCHMIDT, Chicago: I want to thank the discussers. The trials and tribulations of Dr. Dennie call for ready sympathy from anyone who has traveled in South America. Dr. Pardo-Castello is correct in saying that uta and espundia are purely local names. Uta is a Quechua Indian word meaning "gnaw" and is used only in a restricted area of Peru. Espundia seems to be a term used by Spanish veterinarians for tumors with ulcerations.

My purpose in showing the photographs is to call attention to the apparent beneficial influence of high altitude on this group of diseases. Further studies will be conducted on efforts to mimic the effects of high altitude on the body, such as lowered oxygen tension of the blood and polycythemia, by giving the patient those substances which biochemistry has taught us will do those things, namely, vitamins, minerals and enzymes.

# YEASTLIKE DEMATIACEOUS FUNGI INFECTING THE HUMAN SKIN

## Special Reference to So-Called Hormiscium Dermatitidis

ARTURO L. CARRIÓN, M.D.
SAN JUAN, PUERTO RICO

YEASTLIKE dematiaceous fungi from various sources are occasionally isolated in all microbiologic laboratories, and organisms of that type have been described in the literature from time to time under such names as Saccharomyces niger, Schizosaccharomyces niger, Torula nigra, Monilia nigra and Pullularia pullulans. They are generally known as "black yeasts." Our knowledge of this mycologic group in regard to morphology, relationships and pathogenic habits is still incomplete, and the fungi in question are generally considered as contaminating agents having no relation whatsoever with pathologic changes observed in human beings. However, recent observations would tend to confirm that certain species in that group are capable of producing disease. It is the purpose of this communication (1) to review briefly two dermatoses, namely, tinea nigra and chromoblastomycosis, in which fungi of the "black yeast" type have been found to be etiologically important, (2) to present a study of two species of "black yeasts" which were responsible for the infection in cases of the aforementioned dermatoses and (3) to discuss the taxonomic relations of such species in accordance with their morphologic characters.

### TINEA NIGRA

*Clinical Aspects.*—Tinea nigra is a tropical chromophytosis characterized by the development of dark macules, usually on the palmar aspect of the hand and fingers. In the Western Hemisphere this mycosis was first recognized and studied by Alexandre Cerqueira, of Brazil, in 1891, but the discovery was not published until 1916, when his nephew, G. C. Cerqueira-Pinto, described the infection under the name keratomycosis nigricans palmaris.[1] There seems to be no doubt that the so-called

From the School of Tropical Medicine.

Read at the Sixty-Ninth Annual Meeting of the American Dermatological Association, Inc., at Hot Springs, Va., May 26, 1949.

1. Cerqueira-Pinto, G. C.: Thesis, 1916, cited by Langeron, M.: Epidermomycoses tropicales: Tinea nigra et keratomycosis nigricans palmaris, in Darier, J., and others: Nouvelle pratique dermatologique, Paris, Masson & Cie., 1936, vol. 2, p. 361.

keratomycosis nigricans palmaris of Brazil is identical with, or a variety of, the dermatomycosis discovered by Manson in southern China in 1872 and described by Castellani [2] as tinea nigra in 1905.

Clinically, the lesions of tinea nigra vary in color from black to gray, some of them resembling silver nitrate stains (fig. 1 *A*). The macules are roundish, of varied sizes, sometimes slightly elevated and occasionally scaly. They may be discrete or confluent, numerous or scanty. The infection is usually confined to the anterior aspects of the hand and wrist. Although not as common as other chromophytoses, tinea nigra is not to be considered an extremely rare disease. The occurrence of cases in Asia,[2] Java,[2] Brazil,[1] Cuba [3] and the United States [4] is evidence of its widespread geographic distribution. Since 1934, when the infection was recognized for the first time in Puerto Rico, a total of 10 cases have been registered in our clinic.

*Mycologic Aspects.*—The infecting organism is constantly present in epidermal scrapings from the lesions, whence it may be cultured without difficulty on any of the usual laboratory mediums. The morphologic characters in culture correspond closely to those noted in host lesions, and it has been possible to reproduce infection experimentally in man and guinea pigs with the cultured material.[5]

In the epidermal scrapings, the fungus is represented by filaments and blastospores (fig. 1, *B* and *C*). The filaments are refractile and light olivaceous in color, 1.6 to 3 microns wide, engorged in places, long or short, branched, septate at irregular intervals, characteristically tortuous in course and sometimes entangled, forming small masses suggestive of nodular organs. Laterally, the filaments show small conical apiculi around which blastospores occur in small or large groups, sometimes in mosaic arrangement. The blastospores may be fusiform, oval, spherical or irregular in shape; they measure 4.5 to 7.5 by 2.5 to 5 microns, and many of them show budding.

Gross cultures from single spores of the fungus in Puerto Rican cases have been studied on glucose, corn meal and Czapek-Dox agars. For a few days after inoculation, the growth is black, shiny and yeastlike but, by the end of the first week, creeping, moist-looking hyphae may be noted at the periphery. According to observations which have been made, the culture pattern becomes most characteristic about the

2. Castellani, A., and Chalmers, A. J.: Manual of Tropical Medicine, ed. 3, London, Baillière, Tindall & Cox, 1919, p. 2078.

3. Pardo-Castelló, V.: Keratomycosis nigricans palmaris, Rev. argent. dermatosif. **12**:255, 1938.

4. Single case from Florida to be reported by Dr. Louis S. Leland; personal communication to the author.

5. Sartory, R.; Rietmann, B., and Meyer, J.: Contribution à l'étude d'une épidermomycose brésilienne palmaire noire, provoquée par un Cladosporium nouveau, Compt. rend. Soc. de biol. **104**:878 (July 4) 1930.

fourteenth day (fig. 1 *D*). At this time the colonies are generally circular, measure approximately 15 mm. in diameter and are slightly raised in the center, sloping gently toward the border. They show three

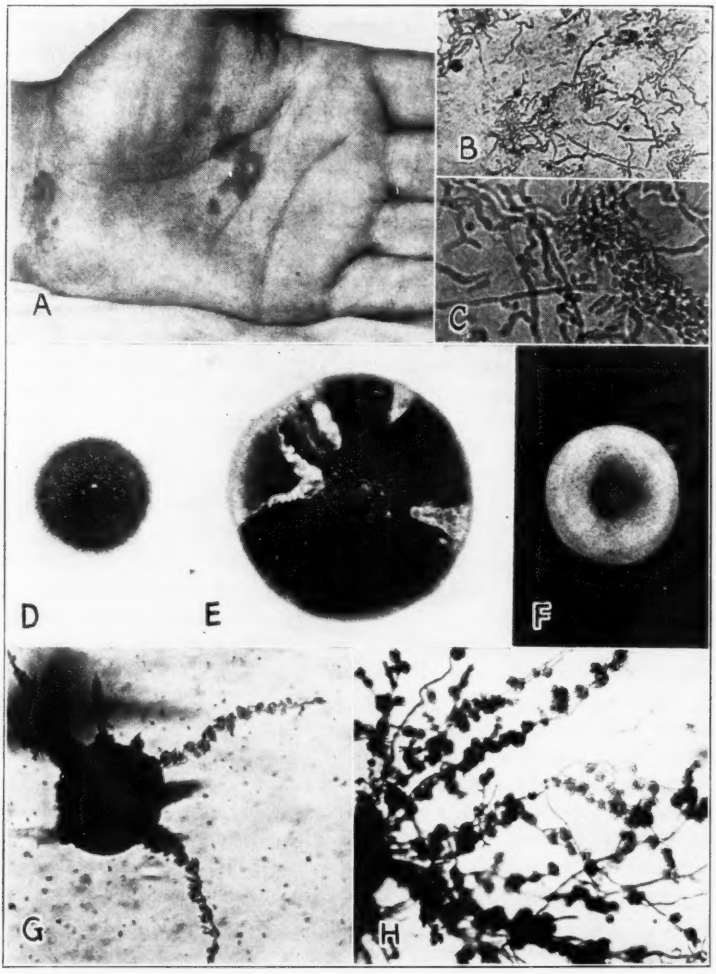


Fig. 1.—*A*, tinea nigra affecting palm and wrist in a white, 15 year old Puerto Rican girl. *B* and *C*, fresh preparations of scrapings from the lesion; fungus represented by filaments and blastospores; *B*, × 150, and *C*, × 430. *D*, Puerto Rican isolate of C. wernecki; culture two weeks old on 4 per cent glucose agar. *E*, culture four weeks old on same medium; note moldy variants. *F*, culture of moldy variant, on glucose agar, three weeks old. *G*, pour plate culture of fungus, on glucose agar, five days old; × 120. *H*, slide culture of fungus, on corn meal agar, eleven days old; × 150.

distinct zones. At the site of inoculation there is a convex irregular black prominence measuring about 3 mm. in width, which still retains its yeastlike appearance. Around this prominence there is a gently sloping, moist-looking black, minutely granular zone about 5 mm. wide. The marginal zone is narrow (1 to 2 mm.), flat, shallow, filamentous, moldy looking and brownish.

After the second week the cultures gradually but progressively lose their moist appearance, the thallus takes on a dark greenish hue and a considerable amount of dry aerial mycelium is developed (fig. 1 *E*). This mycelium may be of two types. One of the types is represented by multiple, rather prominent growths of fine, light gray hyphae which suggest the pleomorphic degeneration noted in some dermatophytes. The fertility of these hyphae is reduced, and sporulation is often abnormal. The other type occurs as dark olivaceous, felty-looking sectors of the mother culture. The light gray moldy variant may be transplanted and kept in the laboratory for many generations without reversion (fig. 1 *F*). On the other hand, the dark olivaceous variant always reverts to the yeastlike form when subcultured.

The microscopic morphologic picture was studied in slide cultures, Henrici's chambers,[6] pour plates, hanging drop cultures and fresh preparations from agar cultures. It was found that the characters correspond essentially to the already noted macroscopic picture; there is always an original yeasty growth with subsequent formation of Candida-like structures (fig. 1, *G* and *H*) and, with aging, a moldy mycelium.

The yeastlike phase is represented by oval, spherical or irregular budding cells, many of which become bicellular by the development of a septum perpendicular to the long axis (fig. 2, *A, B, C* and *D*). Budding may take place at one or both poles (fig 2, *A, B* and *C*) in either the monocellular or the bicellular forms. The small buds grow to a certain size and then fall off, and when they are mature the budding process is renewed. Successive buddings from the same point in the same cell have been occasionally observed (fig. 2 *D*), and chain formations are also observed at times when daughter buds fail to separate from their mother elements after maturity (fig. 2 *A*).

The Candida-like phase is produced through germination (fig. 2, *E* and *F*) of many of the yeastlike cells, which leads to the development of moist, creeping hyphae bearing clusters of blastospores like those produced in Candida albicans (fig. 1, *G* and *H*). The hyphae are long, usually tortuous, branching and septate, with the cell membrane thin and light-colored when young, becoming thicker and darker with age. The

6. Henrici, A. T.: Molds, Yeasts and Actinomycetes, New York, John Wiley & Sons, Inc., 1930, p. 25.

blastospores are produced and shed off, one by one, on tiny, truncated, conical prominences disposed laterally, terminally or on the tip of very short branches (fig. 2, *G*, *H* and *I*), the spores agglutinating at the site of production to form the clusters already mentioned (fig. 1, *G* and *H*). Occasionally some blastospores fail to separate from the mother hypha and, by a series of secondary buddings, they give rise to simple or branching spore chains (fig. 2, *J* and *K*), usually very short, some of the spores bicellular as in Cladosporium (Hormodendrum).[7] When several

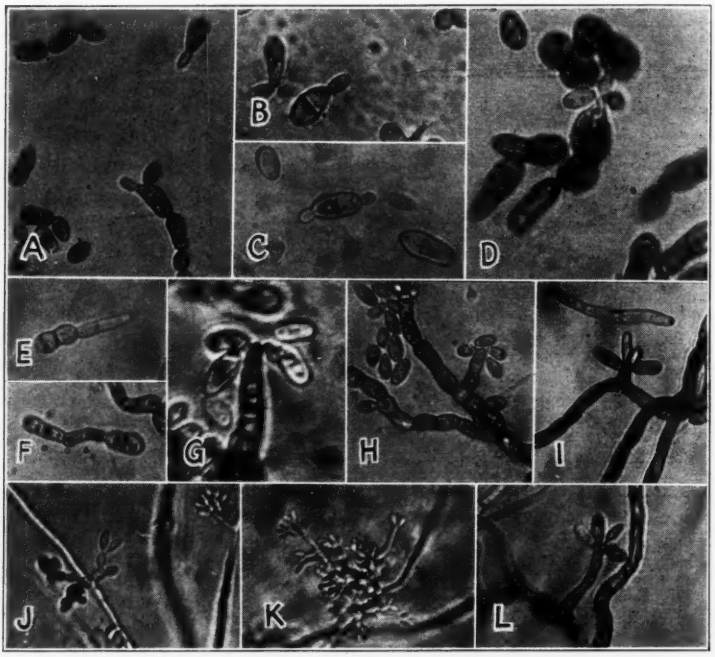


Fig. 2.—Puerto Rican isolate of C. wernecki; microscopic morphologic picture. *A* to *C*, monocellular and bicellular budding forms (*A*, hanging drop culture, on glucose broth, six days old; × 600. *B* and *C*, fresh preparations on glucose agar, two weeks old; × 1,000). *D*, bicellular form showing successive budding at the same point (hanging drop culture, on glucose broth; × 1,500). *E* and *F*, germination phenomenon (hanging drop culture, on glucose broth, ten days old; × 600). *G* and *H*, blastospores produced and shed off on tip of short branches (*G*, hanging drop culture, on glucose broth; × 1,000. *H*, × 600). *I*, blastospores tend to agglutinate at the site of production; note the bicellular form (hanging drop culture, on glucose broth, four weeks old; × 600). *J* and *K*, blastospores in branching chains (slide cultures, moldy variant, on corn meal agar, three weeks old; × 430). *L*, terminal blastospores attached to mother structure (hanging drop culture, on glucose broth, four weeks old; × 600).

7. Thom, C.: Naming Molds, J. Washington Acad. Sc. **30**:49 (Feb. 15) 1940.

adherent spores are terminal in position and secondary buds are not produced at their distal poles, the general appearance of the spore heads might be suggestive of either Acrotheca or Sporotrichum (fig. 2 *L*).[8]

The moldy phase of the parasite is represented by the dry aerial mycelium already discussed in comments on the gross morphologic picture.

*Taxonomic Relations.*—The fungus previously described has been compared with other organisms causing tinea nigra in Brazil, Cuba and the Southern United States,[9] and it has been found that all the isolates are essentially identical in morphologic characteristics, with minor differences of a quantitative rather than qualitative nature. It is presumable, therefore, that tinea nigra in the Western Hemisphere is caused by one and the same fungus species, or varieties thereof. The species has failed to reveal a sexual method of reproduction in culture and, in view of its dark color, it has been classed among the Dematiaceae of the fungi imperfecti.

According to methods of multiplication, the fungus of tinea nigra appears to be related to two important form genera. The yeastlike and Candida-like habits, which are prominent characters of the parasite in culture, point to the genus Pullularia as its closer relation. On the other hand, the production of catenate blastospores, some of them bicellular, and the development, in old cultures, of dry aerial mycelium resembling that of Cladosporium, indicate an additional relationship to the latter genus. This last relationship, however, is not as close as the former. In the first place, catenate sporulation occurs only in scant proportions in many isolates of this species (the Puerto Rican and Cuban isolates), and when more abundant it does not usually reach a high degree of development (the Brazilian isolates). In the second place, most of the bicellular forms which resemble Cladosporium spores are produced by septation of isolated, individual cells during the yeastlike phase of the growth (fig. 2, *A, B, C* and *D*), and it is only relatively few of those bicellular forms that occur as part of the chains of the Cladosporium type arising from fertile hyphae.

According to the foregoing observations, there seems to be no doubt that the etiologic agent of tinea nigra is more consistent with the generic concept of Pullularia than with any other. Notwithstanding this

8. According to Thom,[7] "the identity of *Hormodendrum* with *Cladosporium* has been quite generally conceded . . ."

9. We have been able to study two Brazilian isolates of the fungus, No. 1567 and 1886, from the collection of the Instituto Oswaldo Cruz, due to the courtesy of Dr. Juan E. MacKinnon, of Montevideo, Uruguay, who sent us cultures of those specimens. Two additional isolates, one from a Cuban case and one from a case in Florida, were kindly sent to us by Dr. V. Pardo-Castelló, of the University of Habana, Cuba, and Dr. Norman F. Conant, of Duke University, Durham, N. C., respectively. The fungus sent by Dr. Conant was isolated by Dr. Louis S. Leland.

observation, we feel inclined, at least for the present, to consider this species a Cladosporium on a conventional basis. The fungus of tinea nigra in the Western Hemisphere was originally described by Parreiras-Horta [10] as a Cladosporium, namely, Cladosporium wernecki, and this binomial has been extensively used in the literature. Furthermore, the relation of this fungus to Cladosporium, no matter how remote, is unquestionable, and there is a growing belief among mycologists that the so-called black yeasts, including the Pullularias, would be "but yeast-like growth forms of dematiaceous molds of the type of Cladosporium." [11] Until these organisms become better known in their general morphology, variations and relationships, it will not be possible to establish precise taxonomic positions among them. In the meantime, a transfer of the species just described to the genus Pullularia would only add another synonym to the already confusing nomenclature of the pathogenic fungi, and this is not considered a constructive move at this moment.

### CHROMOBLASTOMYCOSIS

*Clinical Aspects.*—Chromoblastomycosis is a chronic, infectious, granulomatous, apparently noncontagious disease of the skin which may be caused by any of several determinate species of dematiaceous fungi. Discovered by A. Pedroso in Brazil in 1911,[12] its existence has been established in the three Americas, the West Indies, Europe, Africa, the East Indies, Japan and Australia, leaving continental Asia as the only part of the world as yet without reported cases.[13] A review of the literature up to 1947 revealed a total of 151 infections for which the diagnosis of chromoblastomycosis appears to have been made on a sound basis.[13]

Chromoblastomycosis usually affects one of the lower extremities. Beginning as a small papule or warty growth on some part of the foot, the infection spreads gradually upward through the production of satellite lesions. The pathologic process develops slowly, and it is often found that the illness has existed for several years at the time of examination.

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11. Skinner, C. E.; Emmons, C. W., and Tsuchiya, H. M.: Molds, Yeasts and Actinomycetes: A Handbook for Students of Bacteriology, edited by C. E. Skinner, C. W. Emmons and H. M. Tsuchiya, ed. 2, New York, John Wiley & Sons, Inc., 1947, p. 111.

12. Pedroso, A., and Gomes, J. M.: Sobre quatro casos de dermatite verrucosa, produzida pela Phialophora verrucosa, Ann. paul. de med. e cir. **11**:53 (March) 1920.

13. Carrión, A. L., and Silva, M.: Chromoblastomycosis and Its Etiologic Fungi, in Nickerson, W. J.: Biology of Pathogenic Fungi (Annales Cryptogamici et Phytopathologici), Waltham, Mass., Chronica Botanica Co., vol. 6, 1947, p. 20.

In a typical, well advanced case of chromoblastomycosis, the foot and leg are generally swollen and elephantiasic in appearance. The lesions occur in great numbers, especially toward the distal portion of the extremity (fig. 3). They are always more or less prominent and conspicuously varied in morphologic features. Some are nodular; others are tumor-like, and still others take the form of rounded, arciform or polycyclic plaques. Their color varies from dull red to violaceous. Their surface is usually irregular, papillomatous, sometimes lobulated and frequently covered with dirty gray verrucosities, scales and crusts. The lesions of chromoblastomycosis bleed readily when traumatized, and, when pressed, many of them discharge small amounts of caseous material

Fig. 3.—Chromoblastomycosis of six years' duration in a white Puerto Rican man aged 50.

or fluid pus at one or more points. Complicating bacterial infections, and sometimes ulceration, give rise to a characteristic foul smell often perceptible at a distance from the patient. Pruritus and pain are frequent though not constant symptoms.

The deep tissues are not attacked; the draining lymphatic glands may be, but are not usually, involved; metastases through the blood stream are extremely rare, and the general health of the patient is not affected, notwithstanding the partial or total incapacity resulting from the infection.

There is no known drug capable of destroying the infecting fungus in human lesions, and surgical measures, when practicable, constitute the only effective method of therapy.

*Mycologic Aspects.*—The large majority of the organisms causing chromoblastomycosis are dematiaceous molds, with Fonsecaea pedrosoi the most prevalent species in the group.[13] In recent years, however, a few cases of this disease have been associated with fungi that possess a yeastlike phase in the course of their development, in addition to other moldlike characters.[13] Comparative studies of the latter fungi are now being conducted in our laboratories, and in this paper we shall present our observations on one of them which is of special interest for its complicated morphologic picture.

The organism in question was isolated from a case of chromoblastomycosis in Japan and was originally described by Kano as a new species named Hormiscium dermatitidis.[14] Kano was able to reproduce a typical nodule of chromoblastomycosis on the healthy skin of his patient by inoculating locally a suspension of the cultured parasite, and, as will be shown below, the behavior of this species in culture indicates a close relationship with other fungi producing that disease.

According to Kano's description, the morphologic features of his species would be very simple. However, our observations on single spore cultures of the fungus have revealed a rather complicated morphologic picture.

On glucose, corn meal and Czapek-Dox agars the growths are essentially similar to one another: soft, black, moist and shiny during the first few days, later becoming filamentous at the periphery. The colony patterns are characteristic at the end of the fourth week. At this age cultures on glucose (fig. 4 *A*) and corn meal agars are irregularly circular in contour and measure 18 to 27 mm. in diameter; the center is elevated from 1 to 1.5 mm.; the surface is irregular; radial furrowing is shallow or absent; the central zone is granular, soft and somewhat moist looking; the peripheral zone is filamentous, creeping and less moist, becoming brownish at the border; the dry, moldy mycelium is very shallow and faintly perceptible, forming islands or sectors, and some cultures show a dark diffusible pigment. In older cultures a certain part of the peripheral mycelium appears submerged in the agar. On Czapek-Dox agar (fig. 4 *B*), growth is slower, colonies four weeks old measuring about 15 mm. in diameter; the central zone is slightly raised, soft, irregular, granular and black, and the peripheral zone is mostly submerged with the mycelium arranged in characteristic radiating, branching tufts that give to the border of the colony a spiny appearance.

The microscopic morphologic features of the fungus were determined according to the methods already described in the study of tinea nigra. The early growth is always yeastlike in character and consists of a mass

14. Kano, K.: Ueber die Chromoblastomykose durch einen noch nicht als pathogen beschriebenen Pilz: Hormiscium dermatitidis n. sp., Arch. f. Dermat. u. Syph. **176**:282 (Dec.) 1937.

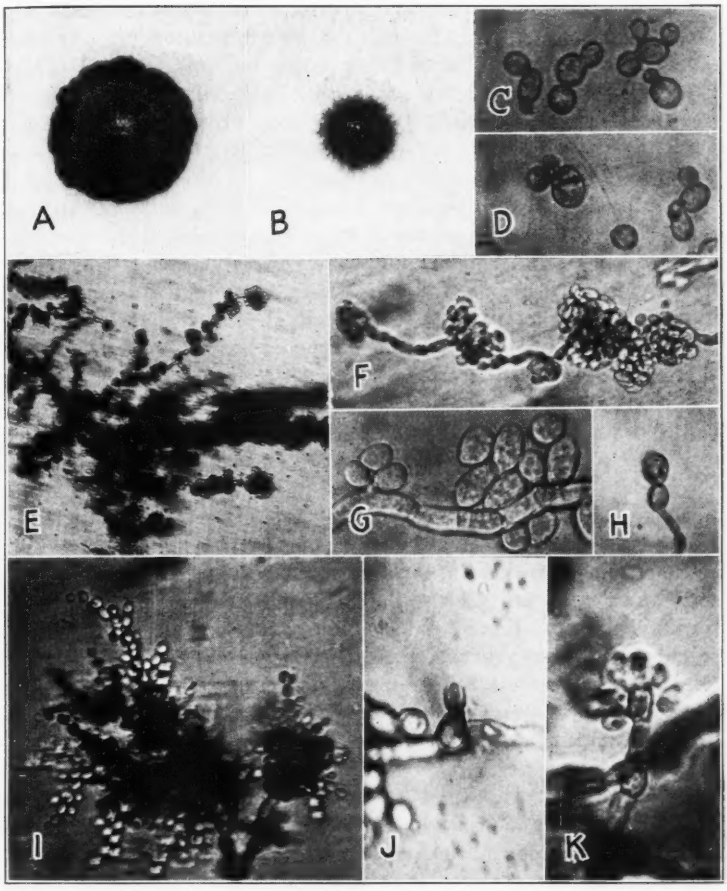


Fig. 4.—Fonsecaea dermatitidis Kano (so-called Hormiscium dermatitidis). *A* and *B*, cultures four weeks old on 4 per cent glucose agar and Czapek-Dox agar, respectively. *C* and *D*, buds formed and shed off at one, two, and occasionally three, different points on the surface of the cell, during the yeastlike phase of the fungus; note double budding from one of elements in bicellular structure (hanging drop culture, on glucose broth, thirteen days old; × 1,000). *E* and *F*, Candida-like phase of fungus; note masses of blastospores along the hyphae (slide culture, glucose agar, three weeks; × 100 *E*, and × 430 *F*). *G*, blastospores are budded out and shed off in succession (slide culture, on glucose agar, one week old; × 970). *H*, terminal chlamydospores (slide culture, on glucose agar, twenty days old; × 430). *I*, blastospores produced in branching chains (slide culture, on corn meal agar, three weeks old; × 430). *J*, flask-shaped conidiophore and conidium of Phialophora type (slide culture, on corn meal agar, three weeks old; × 970). *K*, terminal cluster of spores of Acrotheca type (slide culture, on corn meal agar, four weeks old; × 970).

of spherical or oval budding cells. Evidence of the budding phenomenon may be observed in fresh preparations from this material or in hanging drop cultures. Buds are formed and shed off at one or two, and occasionally at three, different points on the surface of the cell (fig. 4, *C* and *D*), short chains being occasionally produced when the daughter elements fail to separate from the parent cells. Bicellular forms resulting from septation of individual cells are constantly, though very sparsely, observed (fig. 4 *D*).

The production of hyphal structures takes place on germination of some of the yeastlike cells and usually becomes evident at the periphery of the colony a few days after inoculation of the medium. The hyphae irradiate characteristically from the central mass of yeastlike cells and may be easily observed in slide cultures, Henrici chambers and pour plates. They are flexuous, septate, branched and extremely fertile.

As far as has been ascertained, sporulation is only asexual and may take place by different methods. The most conspicuous of these consists in the production of small masses of blastospores both laterally and terminally along the hyphae in a manner somewhat suggestive of that observed for Candida albicans (fig. 4, *E* and *F*). The individual spores vary in shape from spherical to oval (fig. 4 *G*), those of the latter form measuring from 7.5 to 4 by 5.5 to 3 microns. They are budded out and shed off in succession at tiny conical prominences on the hyphal wall (fig. 4 *G*), and, when set free, they tend to remain agglutinated at the site of production, forming the small masses already mentioned (fig. 4, *E* and *F*). In many instances the fertile points are so numerous and close together that the hyphae appear to be completely involved in a sheath of blastospores. All these characters are comparable to those of the yeastlike and Candida-like phases in C. wernecki already described.

Chlamydospores are produced in moderate abundance, their position being lateral, terminal (fig. 4 *H*) or intercalary. They measure from 8.5 to 12 microns in diameter; their cell walls usually become thicker and darker with age, and internal septation sometimes transforms them into bicellular structures. The simultaneous occurrence of these chlamydospores with the small masses of blastospores, already described, on the same hyphal elements would make the resemblance to C. albicans still closer.

It is most remarkable that the fungus under study has revealed three additional types of sporulation that are characteristic of other form genera. Thus, at certain points along the fertile hypha the blastospores are not shed off but remain attached to the hyphal wall and, by subsequent buddings at their distal poles, give rise to branching chains of spores of the Hormodendrum type (fig. 4 *I*). Again, on close examination it will be found that this fungus is also capable of producing flask-shaped conidiophores and conidia indistinguishable from those of

Phialophora (fig. 4 *J*). Finally, the occasional occurrence of clusters of spores attached terminally on a hyphal branch shows, further, a resemblance to Acrotheca (fig. 4 *K*).

*Taxonomic Relations.*—As was already stated, the species we have just presented was originally described by Kano under the name Hormiscium dermatitidis. Indeed, this is another member of the fungi imperfecti, and, like the fungus of tinea nigra, it has a place among the Dematiaceae. However, the morphology of the species dermatitidis Kano, as noted in our laboratory, is essentially incompatible with Hormiscium, and, consequently, a revision of the generic name of this fungus appears to be in order.

It was anticipated that the classification of an organism of this type, showing such a variety of morphologic characters, would not be a simple problem. On the basis of sporulating habits alone, the species in question is apparently related to at least five different form genera, namely Pullularia, Fonsecaea, Hormodendrum, Phialophora and Acrotheca, and its assignment to any of these generic groups could be a subject for debate. After a careful consideration of the different possibilities we have been led to the conclusion that Kano's organism should be placed among the Fonsecaeas. This conclusion was reached on the following grounds. Sporulation of the Acrotheca type in dermatitidis is comparatively too scant and rudimentary to serve as a basis for classification. Inclusion of the species in the genus Pullularia would imply the emendation of the concept of that genus to admit sporulating habits characteristic of several other form genera, which would lead to unnecessary confusion. Similarly, admission to either Hormodendrum or Phialophora could not be effected without confusing emendations, and, in addition, such generic names would be inadequate for a fungus which is predominantly Pullularia in its habits.

The classification of the species dermatitidis Kano as a Fonsecaea may be established on firm biologic grounds. The genus Fonsecaea was specially created [15] and later emended [16] with the chief purpose of gathering into the same group a large number of essentially polymorphous fungi possessing certain fundamental characters in common, namely, (1) ability to produce a specific human disease—chromoblastomycosis and (2) ability to sporulate by three distinct methods which correspond to well established generic groups—Hormodendrum, Phialophora and Acrotheca. The species discovered by Kano is entirely consistent with those characters but possesses, in addition, certain morphologic features that relate it to Pullularia. Since the genus Fonsecaea

15. Negroni, P.: Estudio micológico del primer caso argentino de cromomicosis, Rev. d. Inst. bact. **7**:419 (March) 1936.

16. Carrión, A. L.: Chromoblastomycosis, Mycologia **34**:424 (July-Aug.) 1942.

is already, by nature, a polymorphous group, Kano's organism may be admitted into that group by futher emending the concept of the genus to include species showing supplementary characters of the Pullularia type. Thus, the proper name of the fungus under consideration would become Fonsecaea dermatitidis Kano.

SUMMARY

Attention is called to that large group of fungi, commonly known as black yeasts, many of which are occasionally encountered contaminating cultures in the laboratory. Attention is further called to the widespread belief that fungi of this type are not to be considered significant as etiologic agents of pathologic changes observed in human beings. In this communication evidence is offered to confirm the fact that certain species of this mycologic group are capable of producing disease. A brief clinical discussion of two dermatoses, namely, tinea nigra and chromoblastomycosis, and a description of two fungus species of the "black yeast" type which have been related etiologically to those dermatoses are presented. The morphology of the two species has been carefully studied; their taxonomic relationships have been discussed, and one of the fungi, which was originally described as a Hormiscium, has been transferred to the genus Fonsecaea. I humbly hope that this study will contribute to the promotion of good understanding among workers in the field of medical mycology.

## ABSTRACT OF DISCUSSION

DR. FRED D. WEIDMAN, Philadelphia: Dr. Carrión's remarks on the first topic, tinea nigra, are revealing to all of us. He said that he saw 10 cases in Puerto Rico and that the disease has been discovered in the United States. However, his mycologic studies are far more valuable scientifically. In his views on taxonomy he has always been a conservative. He belongs to that group of mycologists who prefer to bring together certain fungous forms which have been described as separate species and to lump them into a single species; in the present case, the "Hormiscium dermatitidis" of Kano is one of the victims which has been reduced to synonomy. This procedure is in contrast to that of those who announce a new species on the basis of relatively minor differences, which action results in the multitudinous species which beset us. In this respect, Dr. Carrión has been a bulwark in the development of knowledge of the fungi of chromoblastomycosis. The literature shows that he has had an uncanny faculty for discovering Phialophora forms in strains of these black dematiaceous fungi which cause chromoblastomycosis and which hitherto were classified as Acrotheca, Hormodendrum, Phialophora, Fonsecaea and the like. In the present instance he has demonstrated Phialophora cups once again, and figure 4 *J* is the key illustration which indicts Hormiscium dermatitidis. Their attainment has required most exacting work in the laboratory, but his results have proved their worth because they have rationalized the classification of the various forms of fungi which can cause chromoblastomycosis.

As a new departure, Dr. Carrión now extends his specialism for black molds into a relative terra incognita of medical mycology. He takes up the problem concerning two additional forms of these black Dematiaceae, which grow in a yeastlike phase: one isolated from tinea nigra, and the other, from chromoblastomycosis. Thus the black fungi of chromoblastomycosis are revealed in a yeastlike masquerade which must be penetrated and reckoned with when the medical mycologist encounters black (yeastlike or not) cultures that appear to be but saprophytes. Black colonies which are initially yeastlike may prove to be in fact the pathogens in the case.

As an additional complication in chromoblastomycosis, Lewis (*J. Invest. Dermat.* **10**:155 [March] 1948) recently reported a Phialophora (Fonsecaea [jeanselmei]) in a case of maduromycosis. In spite of the fact that this genus has heretofore been incriminated in chromoblastomycosis only, black, madurella-like grains instead of the characteristic pseudobudding cells appeared in the pus and tissue sections. Dr. Carrión's and Dr. Lewis's cases signify that the Dematiaceae in point are as protean as the commoner white Mucedinaceae with which medical mycologists are more familiar. There is not any regularity with which the tissue forms will reflect the form which is taken in culture.

Now that the genus Fonsecaea (Phialophora) has been shown to grow in culture in the yeastlike as well as the mold form (whether with or without demonstrable Phialophora cups) and it has been revealed that in tissue it may appear as pseudobudding cells or as grains, is it too extreme to visualize that the black fungus of tinea nigra, even, belongs to the same group? Perhaps the employment of some special "promoting" substance in culture mediums would elicit Phialophora cups in C. wernecki, too. The success with the use of thiamine, pyridoxine and yeast extract in stimulating the formation of macroconidia in Microsporum audouini (*Mycologia* **39**:200, 1947) illustrates the point, and the employment of such substances (*Tr. New York Acad. Sc.* **11**:281 [June] 1949) could serve as the starting point in studies on C. wernecki.

Finally, I should like to ask Dr. Carrión about the form which the fungous cells took in tissue in Kano's case: Were they the conventional ones which occur in chromoblastomycosis?

DR. V. PARDO-CASTELLÓ, Habana, Cuba: I too have heard Dr. Carrión's paper with great interest. I consider Dr. Carrión one of the foremost living mycologists. There is one point that I want to stress. That is that we dermatologists have been in the habit of considering everything that was not a proved pathogenic organism as definitely nonpathogenic. These organisms are present everywhere—on a leaf, on the floor, etc.

I remember I saw a case of tinea nigra about fifteen years ago in a girl about 15 years of age who had fallen down on the walk of her garden and scraped the palm of her hand; the epidermis came off. In a week she presented a typical picture of tinea nigra.

We have to recognize that many of these organisms which are originally nonpathogenic, living in the soil, on the floor of our homes, on leaves and on grasses, for example, evidently are capable of producing pathogenic conditions of the skin.

# HISTOPATHOLOGY OF THE NODOSE LESION OF ACUTE COCCIDIOIDOMYCOSIS

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ACUTE coccidioidomycosis is a disease with a known etiology in which lesions resembling idiopathic erythema nodosum occur with such regularity that a histologic study of the lesions was undertaken in order to compare them with nodose lesions of the lower leg of questionable or unknown causation.

Gifford [1] was the first to express the opinion that the nodose lesions of "San Joaquin valley fever" or "desert fever" were due to coccidioides. Correlating her observations with his own, Dickson [2] verified the fact that these lesions were manifestations of the primary infection by coccidioides. Dickson and Gifford [3] named the disease the primary type of coccidioidomycosis, thereby differentiating it from the chronic granulomatous and disseminated forms.

In some of the acute types of coccidioidomycosis infection, the earliest workers were confused by the pulmonary changes. Clinically, they were confronted by an acute pneumonic process which was diagnosed roentgenologically on many occasions as tuberculosis. Subsequently, with the appearance of the nodose lesions in the skin and the rapid clearing of the lung fields, the diagnosis was made and a good prognosis given. The red acutely inflamed nodes symmetrically located over the anterior tibial surfaces later involved the thighs, lateral aspects of the hips and the buttocks. The lesions became confluent, tender to pressure and gradually turned purple to brown. They disappeared in about three weeks.

There is a definite predilection for females in that there were 10 female patients to every 4 male patients who had the erythema nodosum

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From the Division of Dermatology, University of Southern California, and Los Angeles County Hospital, Los Angeles, and Kern General Hospital, Bakersfield, Calif.

1. Gifford, M. A.: Erythema Nodosum in San Joaquin Fever, Annual Report of the Kern County Department of Public Health, July 1, 1936 to June 30 1937, Bakersfield California Press, pp. 48-54; Coccidioidomycosis in Kern County California, Proc. Pacific Sc. Cong. **5**:791-796, 1939.

2. Dickson, E. C.: Valley Fever of the San Joaquin Valley and Fungus Coccidioides, California & West. Med. **47**:151-155, 1937.

3. Dickson, E. C., and Gifford, M. A.: Coccidioides Infection (Coccidioidomycosis), Arch. Int. Med. **62**:853-871 (Nov.) 1938.

type of eruption. Greater allergy in the female is ascribed as the reason for the greater percentage of skin lesions in the female. All ages are susceptible

Smith [4] estimated that only 5 per cent, whereas Goldstein and Louie [5] reported 25 per cent, of the patients who had coccidioidomycosis of the acute type acquired erythema nodosum. Although the dusty season is the season of greatest incidence, social and economic conditions seem to

Fig. 1.—The epidermis and cutis show very slight changes. The subcutaneous interlobular septum shows cellular infiltration and vessel wall dissociation. Focal infiltration is evident; × 10.

have no influence on the erythema nodosum type of coccidioidomycosis. It has not been reported in the pure Negro, who usually manifests the

4. Smith, C. E.: Epidemiology of Acute Coccidioidomycosis with Erythema Nodosum (San Joaquin or Valley Fever), Am. J. Pub. Health **30**:600-611, 1940.

5. Goldstein, D. M., and Louie, S.: Primary Pulmonary Coccidioidomycosis, War Med. **4**:299-317, 1943.

granulomatous form. Willet and Weiss [6] reported 2 Negroes in their series of persons with erythema nodosum; however, both had mixed ancestry. The disease has been observed in California, Arizona, Texas, New Mexico, Utah, Mexico, Argentina, Italy and Hawaii.

An eosinophil count of 3 to 7 per cent was frequent, and the sedimentation rate was elevated to between 32 to 56 mm. in one hour as

Fig. 2.—View of involved area in figure 1, showing the vessel with endothelial proliferation and thrombotic cellular intraluminar contents. The muscularis is dissociated by the edema and cellular diapedesis. The adventitia blends with the adjacent tissues. A small radial granuloma adjacent to the vessel wall seems to arise from the perivascular reticulum; × 150.

compared with a normal of 10 mm. in one hour. On bacteriologic examination of the sputum and/or gastric lavage, typical sporulating

6. Willet, F. M., and Weiss, A.: Coccidioidomycosis in Southern California: Report of a New Endemic Area with a Review of One Hundred Cases, Ann. Int. Med. **23**:349-375, 1945.

and nonsporulating yeasts were observed which, on cultures of Sabouraud's medium, grew to recognizable colonies in three or four days. Positive identification of the organism is made on the death of a mouse within ten to fourteen days after intraperitoneal inoculation with 1 cc. of a heavy suspension in saline solution. The guinea pig is also satisfactory for use in identification of the organism, but with it testicular

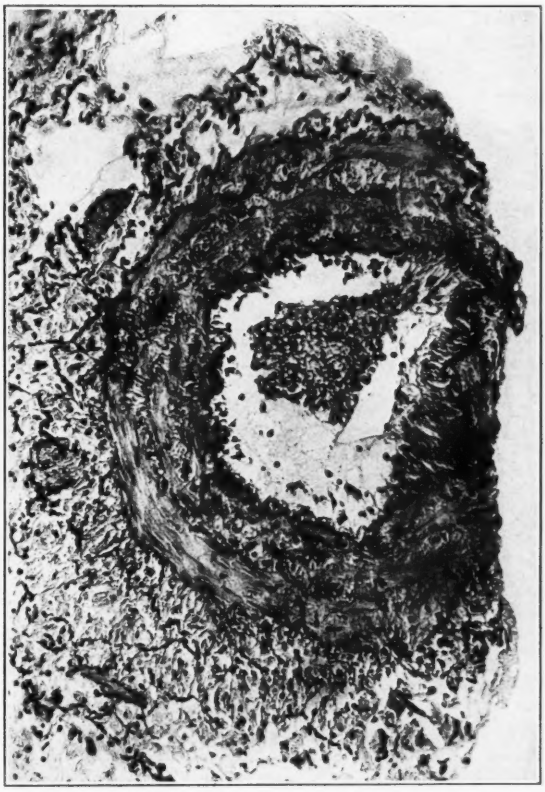

Fig. 3.—Same section as shown in figure 2, stained with Weigert's elastic stain. The vessel shows two laminas of elastic fibers, indicating it to be an artery.

inoculation is done. The spherules of coccidioides are recovered from the viscera or testis of the animal at autopsy. Observation of the organism in a direct smear from the sputum is not conclusive evidence.

Intracutaneous tests with 0.1 cc. of a 1 to 10—and, preferably, because of the intense reaction, a 1 to 10,000—dilution of coccidioidin in patients with acute coccidioidomycosis give strongly positive reactions

in twenty-four to forty-eight hours, indicating a definite sensitization of these patients to Coccidioides immitis. The reaction in the coccidioidin test becomes positive from seven to fourteen days after infection. Jacobson [7] and Kessel [8] produced coccidioidin for the testing of patients and concluded that the substance elicited a specific reaction. A patient with

Fig. 4.—View showing dissociation of the wall of an artery and nests of polymorphonuclear leukocytes adjacent to the fat lobule; × 150.

the granulomatous type of coccidioidomycosis may have a negative reaction to coccidioidin because of anergy present, and it may be neces-

7. Jacobson, H. P.: Coccidioidal Granuloma, Arch. Dermat. & Syph. **18**:562-567 (Oct.) 1928; Immunotherapy for Coccidioidal Granuloma, ibid. **40**:521-540 (Oct.) 1939.

8. Kessel, J. F.: The Coccidioidin Skin Test, Am. J. Trop. Med. **19**:199-204, 1939.

sary in such a case to use 0.1 cc. of a 1 to 10 dilution; Kessel found that in the active cases of coccidioidal granuloma prior to the final fatal stages there was a positive skin reaction. Tuberculous patients as a rule have negative reactions to coccidioidin tests. All the guinea pigs which Kessel inoculated with Coccidioides gave positive reactions to the coccidioidin test, but guinea pigs inoculated with tubercle bacilli all reacted positively to tuberculin but negatively to coccidioidin.

Aronson, Saylor and Parr [9] tested their patients with microsporin, blastomycin, sporotrichin, aspergillus vaccine and coccidioidin and proved that the coccidioidin was definitely specific. In an endemic area, a large

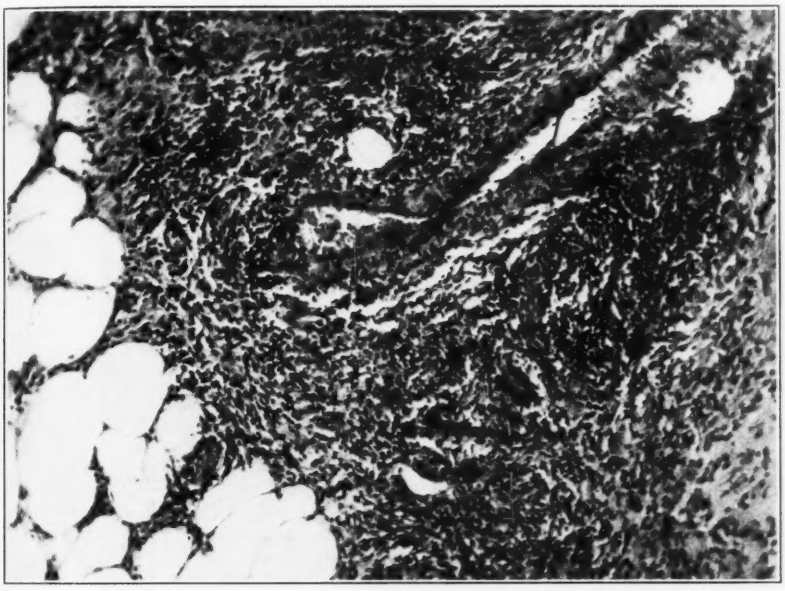

Fig. 5.—Focal areas of polymorphonuclear cells between the septum, containing giant cells and the fat lobule between whose cells are numerous histiocytes and polymorphonuclear leukocytes; × 150.

percentage of the population acquires a positive reaction to coccidioidin. A negative reaction to coccidioidin excludes an infection; a positive one indicates a past or present infection with coccidioides but not necessarily preexistent erythema nodosum.

Faber, Smith and Dickson [10] expressed the opinion that a permanent immunity was set up by the acute form of the disease. They were able to

9. Aronson, J. D.; Saylor, R. M., and Parr, E. I.: Relationship of Coccidioidomycosis to Calcified Pulmonary Nodules, Arch. Path. **34**:31-48 (July) 1942.

10. Faber, H. K.; Smith, E. C. E., and Dickson, E. C.: Acute Coccidioidomycosis with Erythema Nodosum in Children, J. Pediat. **15**:163-171, 1939.

demonstrate positive reactions to skin tests with coccidioidin in patients twenty-one years after the previous outbreak of erythema nodosum. They also reported that the pulmonary observations at autopsy of patients who had had acute coccidioidomycosis but who died of a different condition, were characteristic of pulmonary tuberculosis. The pulmonary lesions were localized at the periphery of the lungs and not at the apexes.

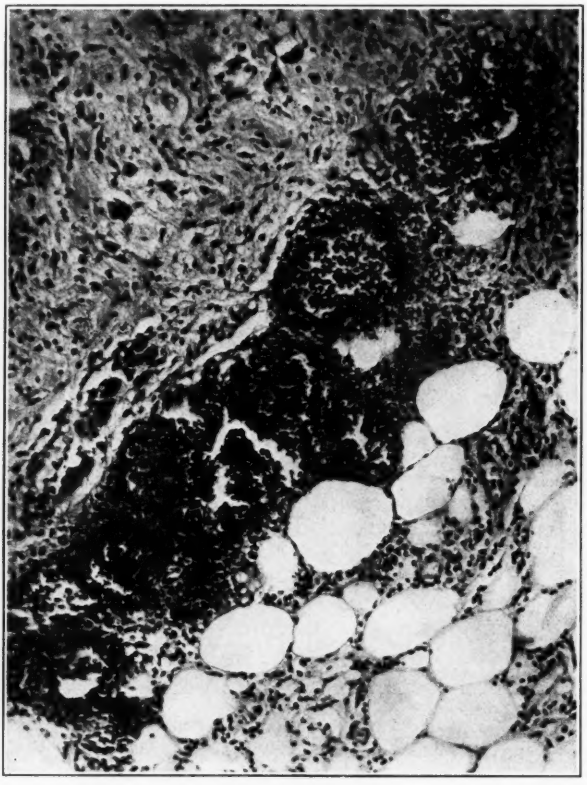

Fig. 6.—Septum with vein in center. The vessel shows endothelial proliferation and thrombus formation. Polymorphonuclear cells are adjacent to the vessel; × 150.

The reaction to tuberculin in their patients with erythema nodosum was negative for 13 of the 15 tested; in 1 it was questionably positive, and in only 1 was it definitely positive. The authors also collected the gastric contents from these patients, which they concentrated and cultured on Sabouraud's medium. Guinea pigs were subsequently inoculated with the material grown. Ten to thirty days were required for recovery

of the organism. Jacobson stated that coccidioidomycosis and tuberculosis could be differentiated only by laboratory observations.

Smith reported on 432 patients who had acute coccidioidomycosis with erythema nodosum, and none acquired coccidioidal granuloma or serious sequelae. He stated that he considered the nodose eruption a manifestation of a nonspecific allergy in which a coccidioides infection

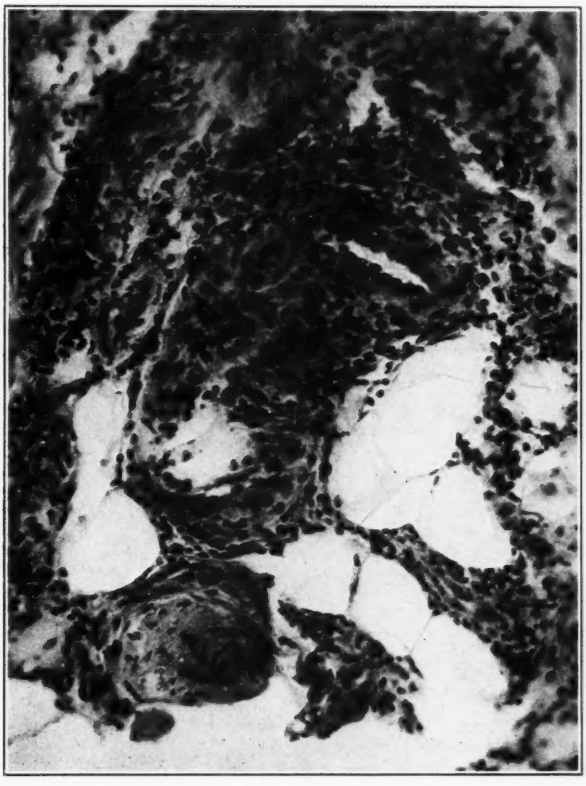

Fig. 7.—Vessel wall involvement by endothelial proliferation. Adjacent to the vessel is a large nest of endothelial cells. Polymorphonuclear cells form a zone around the endothelial granuloma; × 150.

behaved like tuberculosis. He observed that this sensitivity to coccidioidin occurred as a rule from two to seventeen days after the onset of the disease and that erythema nodosum occurred shortly thereafter. Recurrences of erythema nodosum were rare because of retention of the specific allergy; i. e., these patients accquired a permanent immunity and permanently gave a positive reaction to coccidioidin. The hypersensi-

tivity is associated with the change of a negative reaction to coccidioidin to a positive one. If erythema nodosum occurs in the postprimary type of tuberculosis it is probably the result of a loss of allergy after an acute infection such as measles or whooping cough. The return of allergy has the action of a new primary infection in promoting hypersensitivity; therefore, erythema nodosum may develop. Goldstein and Louie differentiated the disseminated granuloma of coccidioidomycosis from the primary infection in this manner: With the disseminated granuloma there were a high complement fixation titer and a low precipitin titer,

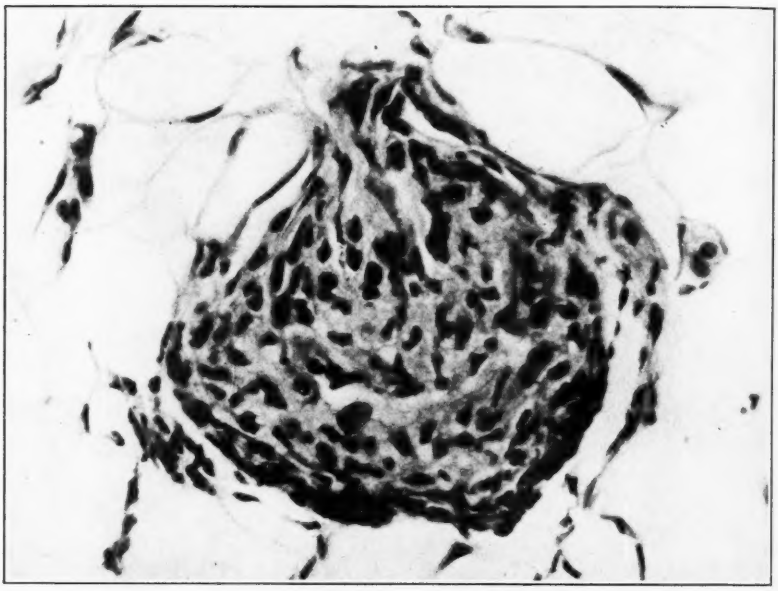

Fig. 8.—In the center of a fat lobule is an endothelial granuloma adjacent to a capillary lying between the fat and the granuloma. The endothelial nest of cells is interspersed with polymorphonuclear cells; × 300.

while with the primary infection there were a low, or absent, complement fixation titer and a high precipitin titer. The complement fixation titer rises with the severity of the infection and is therefore of prognostic value. In the disseminated form, complete fixation at a 1 to 256 dilution occurs. A positive result in the complement fixation test is diagnostic; a negative one does not exclude the infection. These tests are corroborative when the results are positive. The precipitins are lost in a few months, but the result in the complement fixation test remains positive for many months or years.

In the diagnosis of acute coccidioidomycosis, Cherry and Bartlett [11] considered five factors: (1) residence in an endemic area, (2) acute febrile illness with pain in the chest, (3) nonproductive cough, (4) roentgenologic evidence of pulmonary infiltration, plus hilar nodes, and (5) positive reactions in a test with coccidioidin in a dilution of 1 to 1,000 or even of 1 to 100.

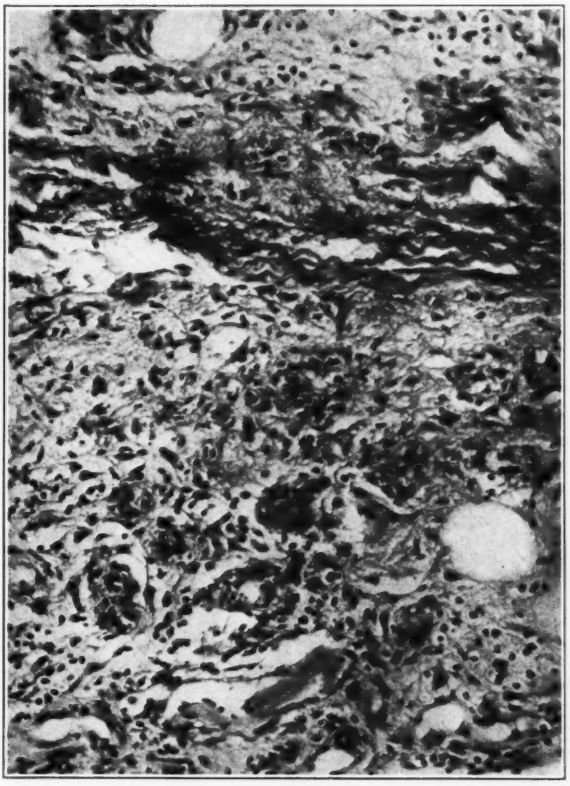

Fig. 9.—View showing fibrillary degeneration of collagen with loss of nuclei and tendency to stain poorly with eosin; × 150.

## REPORT OF PRESENT STUDY

Nine adult patients with nodose lesions were available for microscopic study; (7 were women, and 2 were men). Of these patients 1 had tuberculosis; in 4 the erythema nodosum was caused by streptococci,

11. Cherry, C. B., and Bartlett, A. G.: The Diagnosis of Acute Coccidioides Immitis Infections, Bull. U. S. Army M. Dept. **5**:190-193, 1946.

drugs or some unknown factor, and in 4 the condition was positively acute coccidioidomycosis. The time of biopsy did not seem to influence the histologic pattern, as three biopsies were done two days after the onset of the eruption, and one, twenty-eight days after the onset. In 1 patient with nodose lesions of acute coccidioidomycosis the punch biopsy specimen was removed without any subcutaneous fat. It showed no

Fig. 10.—Histiocytic giant cells in the areas of collagenous degeneration. Reticulated lipid phagocytes are also evident; × 300.

abnormality in the epidermis or cutis. There was a definite similarity among all the specimens.

The epidermis was normal except for a tendency toward flattening of the rete pegs by pressure from below. The upper portion of the cutis showed dilated capillaries and vessels surrounded by zones of edema.

In the subcutaneous fat the sites of greatest change were the interlobular septums. Where the larger vessels were present, especially in the arteries, endothelial proliferation and separation were evident. The muscularis was dissociated by the intense edema and by a polymorphonuclear leukocytic infiltrate. The adventitia blended with the adjacent tissues of the interlobular septum. The lumens of the vessels contained masses of endothelial cells, but complete obstruction was not observed. As observed in sections treated with Weigert's stain, no loss of elastic fibers was evident, but the involved large vessels were seen to be arteries in that they contained a double elastic lamina, one just beneath the intima and the other in the adventitia. The septum showed fibrinoid necrosis, cellular infiltration and fusing edema. This edema caused the septum to assume a syncytial appearance. The cellular infiltration consisted of polymorphonuclear leukocytes and numerous eosinophils. The smaller vessels showed hyalinization of the walls, and adjacent were granulomas of reticuloendothelial cell masses. At the margin of the septum, bordering the fat, were compact masses of polymorphonuclear leukocytes in various stages of disintegration. Interspersed between the polymorphonuclear cell collections were histiocytic phagocytes. Some of them had formed giant cells and had engulfed the degenerated fat.

In the sections stained by Mallory's method the degenerated collagen gave a red-blue color rather than the normal blue-green one. This degenerated collagen was fibrillary in arrangement. In other septums one could see only small capillaries with an adjacent large mass of reticuloendothelial cells.

## COMMENTS

The local clinical appearance and the histologic picture of erythema nodosum, whatever its cause, are the same. This observation is in accord with Brocq's [12] contention that the condition is an objective symptom and is to be classified with the erythemas. The primary changes are vascular and place the disorder in the vasculitis group, as Montgomery, O'Leary and Barker [13] classified it. Histologically, Tachau [14] reported the paucity of findings in the cutis and the predominance of findings in the subcutaneous fat. In my study the most prominent observations were vascular. The dissociation of the larger vessel walls, hyalinization of small vessels, nests of histiocytes, Langhans' giant cells, eosinophils and fibrillary collagenous degeneration have frequently been described. The

12. Brocq, A. J. L.: Quelques réflexions à propos de l'érythème noueux, Bull. méd., Paris **32**:227-229, 1918.

13. Montgomery, H.; O'Leary, P. A., and Barker, N. W.: Nodular Vascular Diseases of the Legs, J. A. M. A. **128**:335-341 (June 2) 1945.

14. Tachau, P., in Jadassohn, J.: Handbook der Haut- und Geschlechskrankheiten, Berlin, Julius Springer, 1928, vol. 6, pt. 2, pp. 617-655.

preponderance of nests of polymorphonuclear cells, many of which were necrotic, and debris of degenerated cells formed a characteristic granuloma. Miescher [15] found radial granulomas which he believed were diagnostic and more readily found by him as a result of his using Bouin's fluid for fixation of the tissues. In the present study, when the fixative was a 10 per cent solution of formaldehyde solution U. S. P., these granulomas were found adjacent to vessels. They could not be differentiated from the granulomas found in periarteritis nodosa as described by Ophüls,[16] Rich [17] and Bergstrand.[18] The last-mentioned author suggested that there was no difference between periarteritis nodosa and erythema nodosum. However, I could find no complete vascular occlusion in the study of any of these erythema nodosum sections. Hyalinization of small vessel walls was evident and accounts for the hemorrhage seen in erythema contusiforme.

The fibrinoid necrosis of the collagen is a partial degeneration and reversible. Therefore, healing takes place without any scar formation. Pautrier and Woringer [19] mentioned the fibrinoid necrosis together with the fusing edema of the collagen in the interlobular septums.

In febrile relapsing nonsuppurative panniculitis, or Weber-Christian disease, the histopathologic features can be divided into three stages, namely, the polymorphonuclear cell infiltrative stage, the granuloma-forming stage with its many forms of cells and the terminal fibrotic stage with sclerosis and scarring. The histopathologic picture for nonsuppurative panniculitis is a diffuse involvement of the entire fat lobule, not limited to the septums or the periphery of the lobule. The foamy cytoplasm of the phagocytic cells gives to the involved tissue the appearance of a sebaceous gland.

Erythema induratum is a tuberculous perivasculitis and is characterized by thrombosis, perivascular tuberculoid inflammation made up of epithelioid and Langhans' giant cells, definite lobulation and replacement atrophy of the fat by lymphocytic infiltration. The central portion of the lobule may undergo caseation necrosis.

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15. Miescher, G.: Ueber Cibazolexantheme, Dermatologica **86**:64-72, 1942: Ueber kutane Formen der Periarteritis nodosa, ibid. **92**:225-245, 1946; Ueber Cibazolexantheme und Cibazolfieber, Schweiz. med. Wchnschr. **73**:521-530, 1943: Zur Histologie des Erythema nodosum, Acta dermat.-venereol. **27**:447-468, 1947.

16. Ophüls, W.: Periarteritis Acuta Nodosa, Arch. Int. Med. **32**:870-898 (Dec.) 1923.

17. Rich, A. R.: Hypersensitivity to Iodine as a Cause of Periarteritis Nodosa, Bull. Johns Hopkins Hosp. **77**:43-47, 1945.

18. Bergstrand, H.: Morphological Equivalents in Polyarthritis Rheumatica, Periarteritis Nodosa, Transient Eosinophilic Infiltration of the Lung and Other Allergic Syndromes, J. Path. & Bact. **58**:399-409, 1946.

19. Pautrier, L. M., and Woringer, F.: Contribution à l' étude histologique de l' érythème noueux, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **45**:1068-1073, 1938.

## CONCLUSIONS

The nodose lesion in acute coccidioidomycosis is an immunity-producing reaction and indicative of a good prognosis.

The histopathologic pattern of the condition is characteristic and similar to that of erythema nodosum, regardless of the etiologic factors.

The lesions of periarteritis nodosa are closely related to those of erythema nodosum and at times cannot be differentiated histopathologically for both conditions show fibrinoid necrosis, histiocytic granulomas and polymorphonuclear and eosinophilic cell infiltration. Similar vascular wall changes are found in both conditions; however, complete vascular occlusion was not found in erythema nodosum.

Erythema induratum and Weber-Christian disease (febrile relapsing nonsuppurative panniculitis) can be differentiated both clinically and histopathologically from erythema nodosum.

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Specimens were obtained from Dr. Ynez Eskelson, Los Angeles; Dr. P. N. Root, Bakersfield, Calif.; Dr. H. P. Jacobson, Los Angeles, and Dr. H. Mackler, Bakersfield. The photomicrographs were made by Mr. L. Madlovsky, and special differential stains were done by Miss Avis Gregersen.

## ABSTRACT OF DISCUSSION

Dr. Leopold Arzt, Vienna, Austria: Nodose lesions have been found in other infections. F. Fischl found these lesions in syphilis and described them as erythema nodosum lueticum. My associates and I observed them in trichophytosis profunda; Bruusgaard gave the name erythema nodosum trichophyticum to such lesions.

I observed this manifestation in a farmer's wife aged 40 who came to the clinic presenting large swollen lymph nodes of the neck similar to those seen in Hodgkin's disease. She had a scar on the right cheek which had followed a recent minor injury. Because she came from a region near Vienna where tularemia is endemic in rabbits, we performed an intradermal test with tularemin and also an agglutination test for tularemia. Both tests gave positive reactions. This patient while under our care acquired erythema nodosum of the lower legs. The clinical photograph and the histologic photomicrograph showed features typical of erythema nodosum. This inflammatory reaction contained many giant cells. We diagnosed our case as erythema nodosum tularemicum.

Therefore I agree that erythema nodosum is not a disease but rather a symptom. It has been found as a result of many etiologic agents, such as bacteria, fungi, viruses and drugs.

Dr. H. E. Michelson, Minneapolis: The problem of nodose lesions occurring on the lower leg is not a simple one. There is always a question of whether erythema nodosum is an entity or part of a syndrome. If we adhere to very strict criteria, I believe there is an idiopathic type of erythema nodosum in which the lesions are characteristic. They are elevated nodes occurring bilaterally but not symmetrically and pass through the evolution we all know. This condition almost never recurs and is not associated with any etiologic factor that can be uncovered.

On the other hand, there are a great many similar lesions of the lower leg which are interpreted as erythema nodosum but really are blotchy erythemas and often are not strictly confined to the lower leg. Such lesions may be provoked by various infections, drugs and the like.

The most important question is that of the relation of tuberculosis to erythema nodosum. The Scandinavian literature, in particular, stresses this relation, and in children it is thought that all erythema nodosum is part of the development of allergy against a primary tuberculous infection. In our material my associates and I have not been able to prove this relation, but our material is exceedingly small, for erythema nodosum is a rare disease in our experience; we have encountered 2 cases among 6,000 new patients.

As far as the pathologic picture is concerned, I do not believe that it is specific. The importance is the location of the reaction in the deep cutis, and when fat is involved the reactions are often similar; however, most nodose lesions do not have even a resemblance to tuberculosis in spite of the presence of giant cells. The specific miliary granuloma, as described by Miescher, may be found in some sections. Dr. Winer's paper is valuable. It demonstrates that nodose lesions originate around blood vessels but, of course, he could not explain why the lesions occur on the lower leg, and this question constitutes one of the baffling aspects of erythema nodosum–like eruptions.

# BENIGN NON-NEVOID MELANOEPITHELIOMA OF THE SKIN (BLOCH)

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MELANOEPITHELIOMA,[1] nevocarcinoma and malignant melanoma are terms used by various authors to describe the most dangerous type of cutaneous cancer, referred to in propaganda on cancer distributed to the laity as the "black death."

My original purpose in drawing attention to the lesions Bloch[2] described in 1927 as benign non-nevoid melanoepitheliomas of the skin was threefold: in the first place, to discuss and attempt to catalog exactly what he described, as there had been radical differences of opinion as to whether the lesions were properly called melanoepitheliomas or basal cell epitheliomas, whether they were "non-nevoid" or whether they were always benign; secondly, to demonstrate that they presented a real problem in clinical differential diagnosis and sometimes in microscopic interpretation as well, and, lastly, to present 3 cases, 1 of which was complicated by the presence of a junction nevus in part of the growth.

However, after painstakingly reading and rereading Bloch's extremely obscure report of the several types of cases grouped together under one title, I trust that I can justify my opinion that the confusion he created does not deserve perpetuation, for the following reasons: 1. Bloch reported two dissimilar types of cases under the one title. 2. While his descriptions were lengthy, they were not cleancut enough to give his readers a definite or clear clinical or histologic picture. 3. As a result, his cases have been confounded with examples of pigmented basal cell tumors and other types of epitheliomas, junction nevi and other types of pigmented nevi, nevocarcinomas and senile verrucae, just to enumerate those most commonly mentioned. 4. Since his cases, with perhaps minor

Read before the Section on Dermatology and Syphilology at the Ninety-Eighth Annual Session of the American Medical Association, Atlantic City, N. J., June 9, 1949.

1. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 7, Philadelphia, Lea & Febiger, 1948, p. 842.

2. Bloch, B.: Ueber benigne, nicht nævoide Melanepitheliome der Haut nebst Bemerkungen über das Wesen und die Genese der Dendritenzellen, Arch. f. Dermat. u. Syph. **153**:20, 1927; Das Pigment, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 1, pt. 1; Pigmented Epithelioma, Schweiz. med. Wchnschr. **57**:45 (Jan. 8) 1927.

differences, fit relatively well into previously described types, there is no reason to give them special designation. 5. His title is bad because one wonders at once what he meant by "benign melanoepithelioma" and because the designation "non-nevoid" was not applicable at least to his second type of cases.

As examples of Bloch's types of cases are encountered relatively frequently and because they may readily be mistaken for various types of pigmented nevi, nevocarcinoma or pigmented basal or squamous cell epitheliomas, as well as other tumors of the skin, a discussion of this problem is timely.

## DESCRIPTION OF BLOCH'S CASES

In his first case, Bloch noted histologically that projecting downward from a thinned epidermis the epithelial columns forming the tumor were perpendicular to the surface and were composed of three different types of cells: basal cells, cells of the spinocellular type (prickle cells), with centrally formed cornified pearls containing little or no pigment, and pigmented cells of dendritic structure which were irregularly interspersed with the basal cells and in many areas exceeded them in size as well as in number. These dendritic cells possessed many irregular processes containing numerous melanin granules and, while dispersed throughout the tumor, were found mostly in the basal parts. In addition to the dendritic cells, there were some cells with short abortive processes and transitions of the cells of the basal type without dendrites. In the connective tissue stroma of the tumor there was evidence of inflammation in certain areas and an enormous amount of pigment. The pigment was found in large globules partly free but mostly within connective tissue cells as well as in the endothelium and in the lumen of the dilated papillary vessels. Bloch expressed the opinion that this case was one of a mixed tumor which not only had basocellular and spinocellular structure but also contained dendritic melanoblasts. On the basis of the histologic changes, he expressed the opinion that the lesion was benign and stated that the tumor might be called a "melanotic benign (precancerous) skin epithelioma with three different cell types."

In Bloch's second case—an observation typical also of his fourth case—there was a solitary papillary nodule, with a dark blue-brown color which gave it a clinical picture similar to that of an early nevocarcinoma, that was progressing slowly. Histologically, it was an epithelial tumor originating from the epidermis and composed exclusively of cells of the basocellular type. The corium was almost entirely free of pigment, and there were no dendritic melanoblasts. Pigment was found mostly in the basal-like tumor cells. This growth Bloch designated as a "benign melanotic skin epithelioma of uniform basocellular type without dendritic cells and almost without chromatophore pigment."

The only difference in his third case from his second case, Bloch stated, was that "there was no pure basocellular character, the chromatophore pigment being present in abundance."

## PERTINENT LITERATURE

In searching the literature for further reports of Bloch's melanoepithelioma, I found only one or two direct references. However, references were made to the lesion in numerous articles dealing with pigmented basal cell epithelioma,[3] superficial epitheliomatosis,[4] cutaneous melanoma, benign epidermal neoplasms [5] and others.

In 1904, Borst [6] described the first intraepidermal growth of an epithelioma in which the tumor cells had spread out into the epidermis from a unicentric origin. Jadassohn [7] in 1926 reported 2 cases, 1 of a basal cell growth and the other of both a basal cell and a squamous cell growth. He emphasized the multicentric origin of these growths. Montgomery [4] added another similar case to that of Jadassohn's second one. He demonstrated varying amounts of melanin pigment in the basal cells of the epidermis, in dendritic cells about the tumor and, rarely, in the tumor cells, as well as a varying number of chromatophores laden with pigment limited to the papillary bodies. Montgomery expressed the opinion that Bloch's first case was histologically an example of the pigmented intraepidermal epithelioma of Borst and Jadassohn and that his second case fulfilled the requirements for verruca senilis and therefore was more properly designated as a delayed epithelial nevus.

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3. (*a*) Eller, J. J., and Anderson, N. P.: Basal Cell Epitheliomas with Excessive Pigment Formation: Their Relation to Melanomas, Arch. Dermat. & Syph. **27**:277 (Feb.) 1933. (*b*) Becker, S. W.: Pigmented Epitheliomas, Correspondence, ibid. **27**:981 (June) 1933. (*c*) Cipollaro, A. C.; Sachs, W., and Brodey, A.: Pigmented Basal Cell Epithelioma, New York State J. Med. **48**:1931 (Sept. 1, pt. 1) 1948. (*d*) Caudière, M.: Recherches sur l'évolution des cellules pigmentaires dans certains épithéliomas envahissant l'épiderme, Ann. d'anat. path. méd.-chir. **3**:119, 1926; (*e*) Recherches sur l'évolution des cellules pigmentaires dans les cancers mammaires envahissant l'épiderme, Compt. rend. Soc. de biol. **93**:1444, 1925. (*f*) Touraine, A.: Les épithéliomas pigmentés de la peau, Ann. de dermat. et syph. **6**:785 (Sept.) 1935. (*g*) Touraine, A., and Renault, P.: Epithéliomas baso-cellulaires pigmentés, Bull. Soc. franç. de dermat. et syph. **42**:644 (April) 1935.

4. Montgomery, H.: Superficial Epitheliomatosis, Arch. Dermat. & Syph. **20**:339 (Sept.) 1929.

5. Becker, S. W.: Benign Epidermal Neoplasms, Arch. Dermat. & Syph. **26**:838 (Nov.) 1932.

6. Borst: Ueber die Möglichkeit einer ausgedehnten intraepidermalen Verbreitung des Hautkrebses, Verhandl. d. deutsch. path. Gesellsch. **7**:118, 1904.

7. Jadassohn, J.: Demonstration von selteneren Hautepitheliomen, Beitr. z. klin. Chir. **136**:345, 1926.

In 1933, Eller and Anderson [3a] reported 2 cases of pigmented basal cell carcinoma and stated, "We prefer the term 'basal cell epithelioma with pigment' rather than 'benign melanoepithelioma of the skin' as suggested by Bloch. The inclusion of the term 'melano' as advocated by Bloch was technically correct. However, epitheliomas were not in any sense 'benign' and the term 'melanoepithelioma' at once brought to mind the most malignant of skin tumors, the melanomas." Eller and Anderson's criticism of the term "melanoepithelioma of the skin," as suggested by Bloch, resulted from a confusion of terms, according to Becker. Becker further stated, "The condition described by Bloch as 'non-nevoid melanoepithelioma' was not the basal cell carcinoma described by the authors. In fact, their figure 4 labelled 'verrucous acanthotic nevus with pigmentation' was identical with case 2 of Bloch, and with a tumor that I have reported. If the term 'epithelioma' were used in its logical sense to designate benign epidermal neoplasms of the skin and 'carcinoma' used to designate malignant lesions, much confusion could be avoided." According to Becker,[5] senile verrucae which have also been designated as keratosis seborrheica, epithelial papilloma and acanthotic or epidermoid nevus were similar to or identical with Bloch's melanoepithelioma.

Cipollaro, Sachs and Brodey [3c] expressed the opinion that it was probable that Bloch's cases were examples of either the nevoid keratoses or intraepidermal epithelial nevi and were not correctly considered as pigmented basal cell epitheliomas.

Under the title "ulcus rodens pigmentosum" Schröpl [8] recorded 2 cases that he believed corresponded in histologic structure to the first of the 4 cases of Bloch.

In a study of 3 cases, 2 of prickle cell and 1 of basal cell epithelioma, Caudière (1926) [3d, e] discussed the process of pigmentation for primary cutaneous epitheliomas. He called them "epitheliomas malpighiens" with symbiotic pigment cells. He made the distinction that they were not primarily pigmentary tumors but pigmented tumors. He cautioned against insisting too much that tumors of the type under consideration have nothing in common with the nevoepithelioma.

Touraine [3f] stated that all clinical types of epitheliomas may become hyperpigmented. He referred to Bloch's cases and those of Eller and Anderson's as examples of nodular epitheliomas. He also commented on 2 cases of Kreibich's (1901) [9] and 1 of Pollitzer's (1905) [10] of xeroderma pigmentosum that had changes similar to those recorded by Bloch.

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8. Schröpl, E.: Ulcus rodens pigmentosum, Arch. f. Dermat. u. Syph. **154**:61, 1927.

9. Kreibich, K.: Ueber geschwülste bei Xeroderma pigmentosum Kaposi, als Beitrag zur Kenntniss des Medularkrebses der Haut, Arch. f. Dermat. u. Syph. **57**:193, 1901.

10. Pollitzer, J.: Eine eigentümbiche Karzinose der Haut (Carcinoderma pigmentosum, Long), Arch. f. Dermat. u. Syph. **76**:323, 1905.

Of 4 cases that were recorded by Halkin [11] 3 were of basal cell tumors while 1 was of a mixed type that developed on a pigmented nevus which remained passive and noncancerous. Thus, the case was not of a pigmented epithelioma but of a relatively benign epithelioma on a nevus. Touraine, however, expressed the opinion that these cases may have been pigmented epitheliomas because in 2 of them at least there were pigmentary cells in the cancerous basal cell portion. It was interesting to note that Touraine placed Halkin's epitheliomas under the nevi undoubtedly as a result of a typographic error, as Halkin was specific in stating that the true basal cell or prickle cell epithelioma can develop on melanotic (pigmented) or achromic (nonpigmented) nevi at the expense of the epidermis of these nevi. It was difficult to trace the separation between epithelioma developed on nevi which remained inactive in the stroma and pigmented epitheliomas as described by Caudière and Touraine. In addition, Aubert,[12] Coomber,[13] Rousset and Lévy,[14] Milian,[15] Oppenheim,[16] Périn,[15] Peyri [18] and Rousset [19] reported nevi associated with pigmented basal cell epithelioma. Nomland [20] and also Nisbet [21] published articles on "Multiple Basal Cell Epitheliomas Originating from Congenital Pigmented Basal Cell Nevi." Nisbet cited

11. Halkin, H.: Les épithéliomas cutanés développés sur naevi pigmentaires, Bull. Acad. roy. de méd. de Belgique **12**:447, 1932; Les épithéliomas cutanés développés sur naevi pigmentaires, Cancer, Bruxelles **9**:241, 1932; Les épithéliomas développés sur nævi pigmentaires et les épithéliomas pigmentés, Paris med. **1**:241 (March 20) 1937.

12. Cited by Milian, G.; Périn, L., and Aubert: Bull. Soc. franç. de dermat. et syph. **39**:1320 (Nov.) 1932.

13. Coomber, R. B.: Basal Cell Epithelioma with Pigment, Secondary to Pigmented Nevus, Arch. Dermat. & Syph. **48**:226 (Aug.) 1943.

14. Rousset, J., and Lévy, A.: Epithélioma granulosquameux en nappe fortement pigmenté, Bull. Soc. franç. de dermat. et syph. (Réunion dermat.) **40**:329 (March) 1933.

15. Milian, G.; Périn, L., and Aubert: Nævi papillomateux, sébacés et sudoripares compliqués de tumeurs à types multiples: épithéliomas baso-cellulaires, baso-sebacés, sudoripares, Bull. Soc. franç. de dermat. et syph. **39**:1320 (Nov.) 1932.

16. Oppenheim, M.: Zentralbl. f. Haut- u. Geschlechtskr. **41**:292 (June 20) 1932.

17. Footnote deleted.

18. Peyri, J.: Epithélioma baso-cellulaire pigmenté à forme verruqueuse et à point de départ naevique, Bull. Soc. franç. de dermat. et syph. **42**:945 (June 6) 1935.

19. Cited by Rousset and Lévy.[14]

20. Nomland, R.: Epitheliomatosis: Multiple, Superficial, Arch. Dermat. & Syph. **20**:754 (Nov.) 1929; Multiple Basal Cell Epitheliomas Originating from Congenital Pigmented Basal Cell Nevi, ibid. **25**:1002 (June) 1932.

21. Nisbet, T. W.: Multiple Basal Cell Epitheliomas Originating from Congenital Basal Cell Nevi, Arch. Dermat. & Syph. **47**:373 (March) 1943.

Pautrier and Archambault and Vigne as having each presented a case with lesions clinically resembling pigmented nevi but with the histologic picture of basal cell epithelioma.

In his paper, Nomland reported a case of multiple basal cell epithelioma originating from congenital pigmented basal cell nevi (intradermal nevi) that he said he could find no counterpart for in the literature. The lesions, however, were looked on as trichoepitheliomas by most of those who studied his case.

In 1935, Peck [22] presented a case of "Bloch's pigmented epithelioma undergoing malignant change." In the discussion, C. Lerner stated that the sections suggested an intraepidermal basal cell epithelioma to him while W. Sachs gave as his opinion that the case fitted better the picture of a verrucous hyperkeratotic hyperplastic epithelial nevus with pigment, with beginning malignant change of the prickle cell epithelioma type.

In 1926 Chambers [23] presented for Stokes a case of basal cell epithelioma. Weidman, in the discussion, commented on the brownish color caused by unusually large pigmented cells in the basal cell layers and in a few of the extensions below that level. He expressed the belief that the lesion was technically a melanocarcinoma but, because of the clinical course and the fact that it did not agree histologically with the picture for Gilchrist's carcinoma, indicated that it was relatively nonmalignant.

Darier [24] classified senile verrucae as delayed nevi. Freudenthal [25] concluded that, since in verruca senilis a characteristic atypical epithelial proliferation took place, these growths were epithelioma-like but not epitheliomas. He stated that he could see no reason for considering them precancerous. Pollitzer [26] considered senile verrucae to be intraepithelial nevi. Eller and Ryan [27] mentioned the possibility of benign hyperplasia of the basal cells similar to benign acanthosis of prickle cells as etiologic in senile verruca. Becker [28] expressed accord with this idea. He stated that he did not believe that the cells can be classed as prickle cells and

22. Peck, S. M.: Bloch's Pigmented Epithelioma Undergoing Malignant Change, Arch. Dermat. & Syph. **31**:760 (May) 1935.

23. Chambers, S. O.: Basal Cell Epithelioma, Arch. Dermat. & Syph. **15**:722 (June) 1927.

24. Darier, J.: Précis de dermatologie, ed. 4, Paris, Masson & Cie, 1928.

25. Freudenthal, W.: Verruca Senilis and Keratoma Senile, Arch. f. Dermat. u. Syph. **152**:505, 1926.

26. Pollitzer, S.: Die seborrhoische Warze, Monatsh. f. prakt. Dermat. **11**:145, 1890.

27. Eller, J. J., and Ryan, V. J.: Senile Keratoses and Seborrheic Keratoses, Arch. Dermat. & Syph. **22**:1043 (Dec.) 1930.

28. Becker, S. W.: Cutaneous Melanoma, Arch. Dermat. & Syph. **21**:818 (May) 1930.

that, therefore, the process is not acanthotic, as was stated by Hookey,[29] who mentioned acanthosis and irregular hyperplasia of the prickle cells in verruca senilis. Becker [30] expressed the opinion that senile verrucae were similar to or identical with Bloch's melanoepithelioma, the only difference being that in Bloch's cases the lesions were of larger size and more decided pigmentation, but that probably there were intermediary stages.

## REPORT OF CASES

CASE 1.—A. S., a man aged 62, was seen in May 1940 because of a slightly raised, smooth, nonhairy pigmented lesion on the lower third of the right leg. It had been present for two or three years but recently had shown evidence of growing larger, darker and also slightly more elevated. It measured 8 by 10 mm. and

Fig. 1 (case 2).—Smooth, slightly elevated pigmented intraepidermal nevus involving the area about and under the great toe nail.

was raised approximately 2 mm. The lesion was excised with the use of procaine (novocain®) hydrochloride, by means of the electric cutting current. Dr. Frank Fraser examined and reported on the section as follows: "This growth, generally designated as Bloch's pigmented benign epithelioma, was strictly speaking, not an epithelioma; it was a benign pigmented acanthoma. The histologic picture harmonized with that of the second type of Bloch's cases in that the growth was an epithelial tumor originating from the epidermis and composed of cells of the basal cell type. There were no dendritic melanoblasts. The pigment was found entirely in the basal-like tumor cells."

29. Hookey, J. A.: Keratoma Senilis and Verruca Senilis: A Clinical and Histopathologic Study, Arch. Dermat. & Syph. **23**:946 (May) 1931.

30. Becker, S. W.: Benign Epidermal Neoplasm, Arch. Dermat. & Syph. **26**:838 (Nov.) 1932.

CASE 2.—R. G., a man aged 43, presented a pigmented lesion on the right great toe of between six and seven years' duration. The lesion involved the area about and directly under the toe nail. The latter was crumbly and seemed to be gradually separating from the nail base. The nail had been cut back on each side, and the pigmentary lesion could be plainly seen to involve the nail base. The pigmentation was smooth, for the most part flat, but seemed to be slightly elevated in its most deeply pigmented portion. The patient stated that during the past year the lesion had increased in size and had become much more deeply pigmented. It had not been painful, but there was some discomfort from shoe pressure, probably due to the thickened and crumbly condition of the nail. The deeply

Fig. 2 (case 3).—Low power view of characteristic changes noted in a benign pigmented intraepidermal nevus; at the site marked by the arrow there is a complicating junction nevus.

pigmented portion of the lesion extended under the nail, and, while there was no bleeding, ulceration or even inflammation present, the appearance of the separation of the nail gave the impression that the condition might be due to the growth taking place underneath. The pigmentation in its darkest portion was black and seemed to be infiltrating deeply into the growth. While the lesion lacked clinically some of the typical features of a well advanced melanotic whitlow, it was thought that it might have been for years a junction nevus that had relatively recently taken on added growth and color indicative of a change to a malignant process. This diagnosis seemed further confirmed as there appeared to be several small pea-sized pigmented areas present that did not seem part of the main

growth, and these were looked on as possible skin metastases close to the primary lesion. It seemed inadvisable to cut into the growth for purposes of biopsy as it would have been difficult to select an area representative of the whole lesion. As no nodes were palpable in the groin or elsewhere, amputation of the toe was recommended. This was done, and serial sections were studied by Dr. David Satenstein. Because of the clinical diagnosis of probable malignant melanoma, many sections were cut and studied, but the picture seen throughout was that of a benign melanoepithelioma of the skin as described by Bloch. This case also fitted into the picture for the second type described by him. No malignant changes were found at any point.

Fig. 3 (case 3).—Medium power view of the cells of a junction nevus complicating the benign pigmented intraepidermal nevus.

CASE 3.—P. D., a married woman aged 57, presented a pigmented lesion measuring 1.5 by 0.65 cm. and of seven to eight years' duration on the right side of the nose near the inner canthus. The area was oval, and the pigment seemed superficially placed, no thickening or depth being present except in one small area of the entire lesion. At this area there was some inflammation at the base and a raised pedunculated or warty lesion was present that had developed within the past six years but had grown noticeably larger only in the past two years. The area was excised in toto and the tissue submitted to Dr. Wilbert Sachs for microscopic examination. He reported: "The tissue consisted of a large thin section, and directly over this in the center was a small lesion. Throughout

the cutis of the large section the vessels were dilated and many of them were filled with blood elements. There was a considerable amount of interstitial edema and a pronounced basophilic degeneration in the subepidermal region. A sparse infiltration of chromatophores was present directly beneath the epidermis. The epidermis was thin and showed no important change. The epidermis of the small lesion was thickened and arranged in anastomosing strands and bands. The surface was verrucous and covered with a densely laminated horny layer. There was considerable pigment in the basal cell margin. At several points in the lower portion of the epidermis were thèques or small nests of nevus cells. These nevus cells had large, round and oval, slightly stained nuclei, definite cell bodies and cell

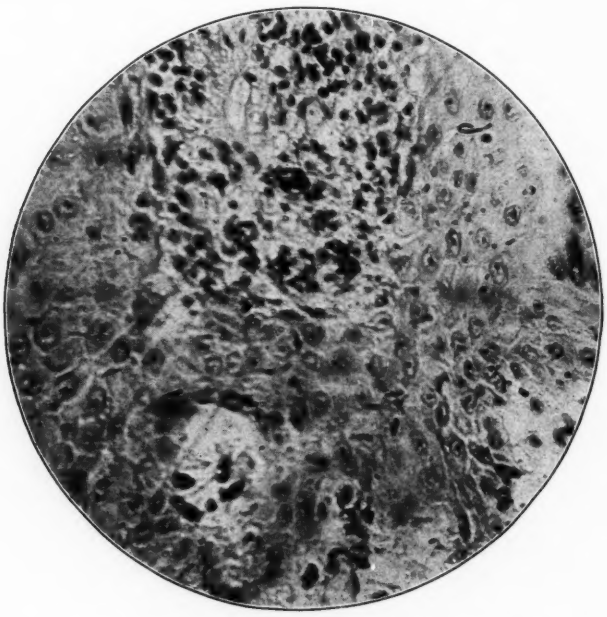

Fig. 4 (case 3).—High power view of the cells of a junction nevus.

outlines. Many contained pigment. There were no nevus cells within the cutis proper. The diagnosis was junction nevus with pigment in an intraepidermal epithelial nevus. There was no evidence of malignant changes."

In this case the clinical diagnosis of Bloch's lesion was entertained, but the raised slightly verrucous portion of the lesion that had suddenly taken on added growth did not seem to fit into that picture. The original sections included only the edge of this portion of the lesion, which probably would have been missed entirely if it had not been especially looked for. This occurrence stresses the point that I have repeatedly emphasized, that the taking of biopsy specimens should be by excision—biopsy specimens should consist of the whole lesion to obviate the likelihood of one's missing parts of a mixed nevus.

COMMENT

The confusion that naturally resulted from the use of such an ambiguous title and the grouping of dissimilar cases under this heading is emphasized by a review of the literature. Bloch used the term "melanoepithelioma" in its strictest sense to describe a pigmentary epithelial tumor. He used the adjective "benign" to indicate that he was simply describing a benign pigmented epithelial tumor. It was an unfortunate choice, however correct, since melanoepithelioma is used synonymously with nevocarcinoma and malignant melanoma and epithelioma has so long been used to designate cutaneous cancer that it would be practically impossible to readjust the term to mean benign epithelial tumors. The "non-nevoid" was undoubtedly added to the descriptions because no nevus cells were present in Bloch's cases. But the term "nevus" is not correctly limited to the designation of lesions containing nevus cells. Since Bloch described a benign pigmentary epithelial tumor, an excellent clearcut title might have been "pigmented intraepithelial (or intraepidermal) nevus." Certainly his second group of cases conformed to this idea, as was attested by Montgomery,[4] Becker [5] and others. Darier,[24] Pollitzer [26] and others classified senile verrucae as delayed intraepithelial nevi. Becker,[31] Montgomery,[4] P. Sachs and Dörffel (cited by Montgomery [4]) expressed agreement that Bloch's second cases fulfilled all the requirements of a verruca senilis. According to Fraser, Satenstein and Sachs the 3 cases herewith presented fitted the concept described by Bloch. There can be no doubt that my cases were examples of pigmented intraepidermal nevi. Clinically the lesions were smooth, slightly elevated, nonhairy and deeply pigmented, and microscopically the changes were essentially epidermal. The lesions were not located at sites usual for verruca senilis, nor did they clinically resemble them in any way. There seems ample justification for looking on the senile verrucae, however, as further examples of intraepidermal growths and because of their peculiar development to consider them (delayed) nevi. The simple classification of nevi we proposed [32] some years ago was based essentially on the location of the lesion either in the epidermis, at the epidermodermal junction or in the cutis. This basis was used because it was realized that clinically there are at least three or four entirely dissimilar-appearing lesions that microscopically are essentially intraepidermal. A classification based on clinical grounds would have been unwieldy and confusing. I comment on this point in detail because it should be understood by all that the pigmented intraepidermal nevi comprise various clinical types.

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31. Becker, footnotes 5 and 30.

32. Traub, E. F., and Keil, H.: The "Common Mole": Its Clinicopathologic Relations and the Question of Malignant Degeneration, Arch. Dermat. & Syph. **41**:214 (Feb.) 1940. Traub, E. F.: Congenital Anomalies (Nevi) and Their Relationship to Cancer and Melanoma, Pennsylvania M. J. **44**:1103 (June) 1941.

The differential diagnosis of my cases was not easy—at least for me. The first case was mistaken for a junction nevus, and in the second case an early nevocarcinoma was suspected. The third case was diagnosed correctly in part and then only because the lesion proved to be a "mixed" nevus—both intraepidermal and junction. Similar experiences must be sufficiently common to warrant a complete excision for biopsy in all cases. I am not referring to the verruca senilis, which usually can be identified clinically without difficulty.

We all realize what a dangerous lesion the junction nevus can be. The pure pigmented intraepidermal nevus is benign so far as we know. The fact that clinically these two lesions may resemble and hence be mistaken for each other may further explain the lack of more uniformly serious consequences that occurred after the use of freezing, chemical applications and other dangerous measures when such remedies were formerly employed. Reasons for not employing such remedies at the present time should be obvious to all.

One of the chief points made in presenting our classification for nevi was that it was a reliable guide as to prognosis. The junction nevus might terminate as a nevocarcinoma; the intradermal nevus always remained benign, and some types of intraepidermal nevi might terminate as epitheliomas. One of the criticisms was that this contention was not always true. I wish to point out again that when apparent exceptions to these rules occur, a "mixed" lesion has been overlooked. Not only may the lesion have been a "mixed" nevus but also it may be pointed out that many authors have recorded the development of epitheliomas at the expense of the overlying epidermis of nevi which take no part in the process. Thus one must be extremely careful before concluding that an intradermal nevus, for example, can terminate as a basal cell epithelioma, as was recorded by Nomland.[20] The very fact that he could find no counterpart for his case in the literature should have made him suspicious, because there is really very little new under the sun.

As there is considerable difference of opinion as to whether the dendritic cell exists as a special cell or as a modified basal cell, among other possibilities, a discussion of the various controversial cell types mentioned by Bloch is omitted as irrelevant to the purpose of this communication.

## SUMMARY AND CONCLUSIONS

Reasons are given why Bloch's title "benign non-nevoid melanoepithelioma of the skin" should not be perpetuated.

His first case fulfilled the histologic requirements of a pigmented intraepidermal epithelioma of Borst and Jadassohn with both basal and squamous cell growths in situ.

His second group of cases presented a picture similar to or identical with that of verruca senilis.

The title "pigmented intraepidermal nevus" is suggested for cases falling into his second (and much more frequent) category.

The importance of recognizing that benign pigmented intraepidermal nevi exist and that they may readily be mistaken for junction nevi or, less likely, even for intradermal nevi and nevocarcinoma justifies the time spent in their study.

Pigmented intraepidermal nevi constitute only cosmetic deformities and not a cancer hazard. Their removal is indicated only for diagnostic purposes.

The difficulties attending clinical diagnosis warrant complete excision for biopsy in practically all cases.

Excision for biopsy is recommended so that one can avoid missing "mixed" nevi which might not be included in small punch biopsy specimens and for the general safety of the patient, which might be jeopardized if the lesion were cut into rather than removed in toto.

The independent presence of epitheliomas and pigmented nevi in the same lesion is stressed.

The relatively frequent occurrence of "mixed" nevi in the same growth is reemphasized.

140 East Fifty-Fourth Street.

## ABSTRACT OF DISCUSSION

Dr. W. M. Sams, Miami, Fla.: Dr. Traub deserves our commendation for attempting to unravel the various names which have been proposed for the benign pigmented intraepithelial nevus. The attempt to select better names for some of the benign lesions and tumors of the skin is desirable. In certain respects, Dr. Becker's use of the term "epithelioma" to designate the senile verruca is logical, but the fact that the same term has been used to indicate a malignant lesion for so long will lead to confusion if his suggestion is adopted.

This problem concerns every dermatologist daily and will increase as long as our educational campaign regarding tumors and cancer continues. I am sure that each of us is consulted daily by a person with a nevus of some type—usually the intradermal nevus, which is accepted as nonmalignant. Such a patient needs treatment, psychologic treatment primarily. He has cancerophobia, and this can be cured only by convincing him that you can recognize the lesion clinically and that no treatment is indicated, or, when this is impossible, by making a microscopic examination, usually with removal of the entire lesion for the biopsy.

Treatment, however, is complicated by the cosmetic problem, since many of these patients are women and frequently nevi are located at a point where total excision of the lesion for biopsy is difficult. Even the punch method of taking specimens, in certain areas, leaves a poor cosmetic result. This objection holds especially true for the nose. There, and on the edge of the eyelid, excision for biopsy is difficult. Many lesions, however, are fortunately located where they can be easily excised, and the procedure is simple. Where difficulties are encountered, it is permissible to use the slice method of taking tissue, removing only that portion of the tumor which projects above the surface. This method affords opportunity for histologic examination, and it may be found that what may have been considered an intradermal nevus may prove to be some other type of benign tumor or a skin cancer. In any event, correct therapy can then be instituted.

There are times when excision of the pigmented nevus may not be the best method of approach. In 1 case presented by Dr. Traub, in which a man had his great toe removed, some functional difficulty naturally ensued. A careful review, the judicious removal of tissue and a subsequent histologic examination constitute the only acceptable approach in dealing with this problem.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I am in accord with Dr. Traub's emphasis on the epithelial nevoid origin of these lesions and also with his contention that we should not carry on Bloch's term, which is confusing. I also believe that the term "benign melanoma" is confusing. Designation of verruca senilis and/or seborrheic keratosis has been confused with senile keratosis in recent articles. Verruca senilis can be distinguished clinically from senile keratosis in the great majority of cases. When there is doubt, a specimen for biopsy can be taken. Intraepidermal epithelioma of Jadassohn is a relatively rare lesion; yet, in going through my files, I found I had 12 cases, in a few of which the lesion apparently arose from a verruca senilis. The incidence of epitheliomatous changes in verruca senilis is less than 3 per cent in contrast to a 20 per cent or more incidence of epitheliomas arising from senile keratosis. Intraepidermal epithelioma of Borst and Jadassohn resembles clinically the lesion of superficial epitheliomatosis. If one suspects a lesion to be a melanoepithelioma, it should be excised widely. A great many lesions of verruca senilis have been removed because they were suspected to be malignant, when histologically they were proved not to be.

DR. E. F. TRAUB, New York: The type of lesion under discussion is important because it can be mistaken for a junction nevus, a nevocarcinoma or other similar pigmented growths. As it is a relatively benign lesion it is better to make the mistake of removing this benign lesion rather radically than to remove inadequately a dangerous lesion on the basis of the mistaken idea that it is a benign pigmented epithelial nevus. The dermatologist, it seems to me, is the one specialist particularly trained to recognize clinically various growths of the skin preoperatively, and, while mistakes occur in all specialties, I am convinced that dermatologists at least avoid many of the more stupid and gross errors likely to be made by surgeons.

To avoid any error, since most of the lesions are usually extremely small, excision for biopsy with only a moderate margin of normal tissue included in the specimen is recommended. This can be followed if necessary by a more radical procedure at a later date if that is indicated by the histopathologic picture. Since most of the lesions under discussion are essentially cosmetic deformities, it is not surprising that one can accomplish an excellent cosmetic result by excision of the lesion for biopsy better than can be secured by treatment of a clinically identified lesion by repeated freezing or desiccation or some other type of similar application. I believe the term suggested, namely, benign pigmented epithelial nevus, is much better than the one suggested by Bloch. I trust that this will be used in the future for these lesions, as at least some of the confusion will thus be eliminated. The lesions described by Bloch are simply types of intraepithelial nevi and should not be confused with ordinary basal cell carcinoma or nevocarcinoma, as they have been in the past as a result of the use of Bloch's title.

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## NOTICE

The index for Volume 61 will be mailed with the July 1950 number.

# Society Transactions

## CHICAGO DERMATOLOGICAL SOCIETY

S. W. Becker, M.D., *President*

L. F. Weber, M.D., *Secretary*

*Jan. 19, 1949*

**Metastatic Carcinomatosis.** Presented by Dr. D. V. Omens and (by invitation) Dr. Harold Omens and Dr. S. Barsky.

H. R., a 45 year old Negro woman, complained of painful masses in both groins of six months' duration and swelling of both legs of two weeks' duration. The lesions had first developed as "pimples" in both groins while the patient was receiving arsenotherapy for late latent syphilis in February 1948. She has had recurrent edema of the whole leg for the past three years, worse on the right than on the left.

One year ago she had a sore throat of two weeks' duration. A diagnosis of diphtheritic laryngitis was not confirmed at that time. The patient has had a nasal voice since then.

On examination there are seen to be bilateral, tender, purplish red tumors, many of which are ulcerated and fluctuant, in both inguinal regions. There is moderate lymphadenopathy in the left supraclavicular fossa and right axilla.

Gynecologic examination yielded no information as to the source of the primary focus. Repeated physical and roentgenologic examinations failed to reveal the source of the primary carcinoma.

The urine showed albumin, 2 plus. The examination of the blood showed hemoglobin, 52 per cent; erythrocytes, 3,160,000, and leukocytes, 13,100, with 81 per cent polymorphonuclear cells, 1 per cent polyeosinophilic cells, 10 per cent lymphocytes and 8 per cent monocytes. Blood chemistry showed 5.8 mg. of total protein, with 3.0 mg. of albumin and 2.8 mg. of globulin per hundred cubic centimeters. The amount of nonprotein nitrogen was 45 mg. per hundred cubic centimeters. Examination of spinal fluid gave a negative reaction. The reaction in the Frei test and results of a smear for Donovan bodies were negative. The Kahn and Wassermann reactions were positive on December 28 but negative on January 5 and 9. Roentgenograms of the pelvis showed no osseous pathologic changes.

Histologic examination of a biopsy specimen from the right supraclavicular lymph node showed infiltrating anaplastic epidermoid carcinoma, and that of a specimen from the mass in the right inguinal region, carcinomatosis cutis.

### DISCUSSION

Dr. Francis W. Lynch, St. Paul: Since only inadequate examination is possible at such a large meeting, one must depend on the reported observations which have already led the presenters to a diagnosis with which it is thus difficult to disagree. If the cutaneous involvement is secondary to that in the nodes, one would like to demonstrate a primary malignant condition as a cause for the regional adenopathy. If involvement in the nodes represents distant, rather than regional, metastases, it is difficult to account for the symmetric involvement when

other regional nodes are apparently not involved. The microscopic sections of metastases sometimes demonstrate the nature of the primary site, but I am told that they do not do so in this case because of the low degree of differentiation. Summing up all these points, I find it difficult, though not impossible, to interpret the cutaneous changes as those of a metastatic malignant process. Cannot dermatofibrosarcoma protuberans be a possibility, with the cutaneous changes preceding the deeper involvement seen here? The clinical features are noncharacteristic but fairly acceptable for that diagnosis, especially the sites, symmetry and possibly the previous lesion higher on the trunk.

DR. M. R. CARO: I believe that a diagnosis of dermatofibrosarcoma is entirely unacceptable histologically. The section showed very sharply outlined nests of cells which to me were more suggestive of melanotic cells than anything else. I think that the lesion will turn out to be a melanoma rather than some type of epidermal malignancy. I cannot explain the presence of the same type of lesion, which was diagnosed elsewhere as being malignant, in the subclavicular area.

DR. S. W. BECKER: I was of the same opinion. The fact that the cells were round and oval and somewhat separated made me think of a nonmelanotic melanoma. There is a case on record (Selig, S.: Metastasis to Groin Four Years Before Appearance of Primary Lesion on Heel, *Am. J. Cancer* **20**:594, 1934) of a patient who had a swollen lymph node in the inguinal region, of which a microscopic diagnosis of melanoma was made. Very careful examination of the limb revealed no primary tumor. Four years later the person manifested a small tumor on the foot, which proved to be the primary melanoma. This patient may have an inconspicuous lesion, possibly about the genitalia, which is the primary tumor. I could find no tumor on the legs or feet.

**Porphyria with Sensitivity to Sunlight.** Presented by DR. THEODORE CORNBLEET and (by invitation) DR. H. SCHORR and DR. S. BARSKY.

F. F. is a 41 year old Negro woman who was first diagnosed as having porphyria in July 1947. She has had two other episodes similar to the present one, one in September 1946 and one in July 1947. These have been associated with acute cramping pains in the lower part of the abdominal region, nausea, vomiting, weakness and the presence of wine-colored urine.

The patient had one episode of jaundice after the birth of her first child twenty-two years ago. During the past twenty years she has had nausea and vomiting on exposure to varying amounts of sunlight. Chloroform extraction of the patient's, her brother's and her sister's urine revealed porphyrins. The urine of the patient's son and of her daughter did not contain porphyrins.

Administration of tripelennamine (pyribenzamine®) hydrochloride, 50 mg. four times a day, was started Jan. 5, 1949 and continued for four days. During this interval the patient had a hallucinatory state which continued for two days after the use of tripelennamine was discontinued.

On examination there are a few scattered follicular, erythematopapules on the trunk. The neurologic examination today revealed essentially normal conditions. A few days ago the Babinski reflex was elicited on the left side. Heart, lungs and abdomen are essentially normal. The blood pressure is 210 systolic and 120 diastolic.

The urine gave no reaction for albumin or sugar and a 4 plus reaction for urobilinogen. The urine turned red on standing. The results of the chloroform extraction test were positive for porphyrins. Examination of the blood showed

hemoglobin, 94 per cent; red cells, 5,000,000, and leukocytes, 11,600, with 97 per cent polymorphonuclear neutrophils, 1 per cent lymphocytes and 2 per cent monocytes. The roentgenograms of the heart and lungs revealed no abnormalities.

One of the patient's sisters has chronic urticaria associated with porphyrinuria.

DISCUSSION

DR. LOUIS A. BRUNSTING, Rochester, Minn.: I am not acquainted with the incidence of porphyria in the Negro. This patient presents a history of distinct episodes of acute porphyria; the sensitivity of the skin to sun is not clearcut, and the patient's history seems to have been built up somewhat by leading questions. Patients with acute porphyria occasionally may show hyperpigmentation or even urticarial reactions, but, as a rule, as in Waldenström's experience, there is no cutaneous reaction in acute porphyria. The finding of abnormal porphyrins in the urine of the siblings—especially the demonstration of porphobilinogen—is of interest. This is not generally present in the cases of so-called congenital porphyria, but many of the distinctions between congenital and acute porphyria are being abolished. Porphyria is a metabolic fault on a hereditary basis with variable symptomatology. It seems that there are many more latent cases of porphyria than is generally appreciated.

DR. STEPHEN ROTHMAN: I should like to call attention to the very lucid article of L. Szodoray in *Dermatologica* (**90**:233, 1944) on simple laboratory tests for separation of the different porphyrin isomers.

**Successful Treatment of Lupus Vulgaris with a Combination of Calciferol (Vitamin $D_2$) and Streptomycin.** Presented by DR. THEODORE CORNBLEET and (by invitation) DR. D. COHEN and DR. D. MUSGRAVE.

A. S., a 13 year old Negro boy, is presented to show the results of therapy with calciferol and streptomycin.

The patient has had a granulomatous lesion of the nose of eight years' duration, diagnosed as lupus vulgaris (Dr. M. R. Caro) after numerous biopsy specimens had been taken. The Mantoux tests gave a strongly positive reaction at a dilution of 1:10,000.

Prior to recent admission to the Cook County Hospital, the patient had received various types of therapy, including administration of a concentrated vitamin D preparation, with little or no benefit. On admission to the hospital in August 1948, he received 0.5 Gm. of streptomycin twice daily and calciferol in doses of 50,000 units one day and 100,000 units on alternate days for nine weeks.

He was presented to the Society in October 1948 and again today that we might observe the results of therapy.

**Lupus Vulgaris Successfully Treated with a Combination of Streptomycin and Calciferol (Vitamin $D_2$).** Presented by DR. F. E. SENEAR and STAFF.

DISCUSSION OF CASES OF LUPUS VULGARIS

DR. OTTO H. FOERSTER, Milwaukee: Many persons are reported in the literature as having had deformities corrected by plastic surgery with recurrence of lupus nodules even many years after the original disease had apparently disappeared. It occurred to me that perhaps in calciferol we have an agent to use before plastic surgery is attempted and which may help to prevent recurrence of the lesions. I have used it for this purpose, but too recently to judge of its value.

**Nonpustular Psoriasis of the Hands.** Presented by DR. F. E. SENEAR and STAFF.

M. P., a 42 year old woman, was seen on Dec. 28, 1948, complaining of scaling and fissured callosities of the hands, especially on the knuckle areas, of about eighteen months' duration. Arthritic symptoms in the hips had been present for a few years.

Examination revealed several circumscribed, hyperkeratotic oval plaques over the knuckle areas with slight scaling and some superficial fissuring. Also there were oval scaling plaques along the sides of the fingers and palms, some of them saucerized. The elbow and knee areas revealed a slight, dry, mildly scaling hyperkeratosis not typical of psoriasis; Auspitz' phenomenon (presence of bleeding points on scraping) was not demonstrable. The scalp showed no evidence of psoriasis. The finger nails were covered with coats of nail polish. Biopsy of a callosity on a knuckle revealed the following features: The epidermis was acanthotic to a horizontal line below. Hyperkeratosis with parakeratosis was present. The granular area was interrupted, being absent beneath areas of parakeratosis. The suprapapillary rete was thinned. In the rete mucosum beneath the stratum corneum were small intraepidermal abscesses containing round cells (Monro's abscesses). The papillae were elongated and contained blood vessels which were surrounded by round cell infiltrate. The findings were diagnostic of psoriasis.

DISCUSSION

DR. CLEVELAND WHITE: The clinical appearance and the sections were characteristic of psoriasis. This case brings out the fact that occasionally one observes a few discoid lesions on the palms which may turn out to be psoriasis with no psoriasiform lesions elsewhere.

DR. CLARK W. FINNERUD: I do not think many people will agree with me, but I rather doubt that the condition is psoriasis. I have seen the same picture a good many times occurring at and after the menopause. This patient stated that her menstrual periods ceased two and one-half years ago and prior to that had always been very regular. She says that ever since the onset of the menopause she has been extremely nervous, in spite of the fact that she does not show it. I think that this condition is a postmenopausal type of keratodermal neurodermatitis, in spite of the fact that histologically it is a beautiful example of psoriasis. There is no history of arthritis. Clinically the condition involves some areas of psoriasis, but I do not think it is psoriasis.

DR. JOHN F. MADDEN, St. Paul: I agree with Dr. Senear that this is psoriasis of the palms. Psoriasis can remain localized on the palms for many years. This site closely follows the scalp and nails in frequency as a point of localization of psoriasis.

DR. EDWARD A. OLIVER: I agree with Dr. Senear. We have been seeing this condition in our office practice for the last four or five years. We feel that cases of this kind have been neglected and misdiagnosed as eczema climactericum or ordinary eczema. This condition occurs in men just as well as in women. I have 3 cases in women, and in most of them there were typical psoriatic lesions which responded beautifully to application of anthralin ointment.

DR. FRANCIS W. LYNCH, St. Paul: Such cases always arouse controversy. My reaction here is like that of Dr. Finnerud, that we are dealing with a psoriasiform dermatitis rather than with psoriasis. I do not believe that microscopic study can always lead to differentiation between psoriasis and eczema nor that it does so in this case. My conception of this case is that it is psoriasiform neuro-

dermatitis with keratodermic palms occurring in an emotionally disturbed woman with estrogenic deficiency.

DR. S. J. ZAKON: In keratoderma climactericum of Hauxthausen there are, besides the symptoms of menopause, obesity, hypertension, keratoses, arthritis and a normal basal metabolic rate. If all four findings are observed, keratoderma of Hauxthausen is present; if any one is seen alone, psoriasis or lichen simplex chronicus must be considered in the differential diagnosis.

DR. FRANCIS E. SENEAR: If this condition is keratoderma climactericum I should like to say first that I think the male menopause is very, very common and that premature menopause is much commoner among women than I had thought, because my associates and I have seen a very large number of these cases in men and a good many in women who were not near the menopausal age. Our experience with the Hauxthausen type of keratoderma is that the feet are commonly involved, but we have not seen involvement of the feet in our cases. Our experience with the Hauxthausen type is that the keratoderma has been present on the ends of the toes and the digits. We never see that situation in these cases. That disorder is also seen in obese women. I could not feel at all that the present case was a keratodermic change due to the menopause. As far as its being neurodermatitis is concerned, I think that there is room for discussion, but we have seen patients who presented the hand picture alone and who eventually acquired what to us was clinically typical psoriasis on other parts of the body. We have also had repeated histopathologic examinations made of specimens from these patients, and, while it is undoubtedly possible to find difficulty in some instances in differentiating psoriasis from neurodermatitis histopathologically, it does not seem that this occurrence should happen consistently. With reference to biopsy material from 1 of the cases presented by Dr. Caro and me in our original report, a slide was sent without history or diagnosis to both Dr. Weidman and Dr. Montgomery, and both reported an unequivocal diagnosis of psoriasis.

I do not mean to be argumentative. The clinical picture is very typical, as was pointed out in our original article, with involvement on the sides of the fingers and sometimes on the palms, with an isolated type of hyperkeratosis and very prominently, as this woman showed well, a saucer type of depression in the lesions along the sides of the digits. Likewise there are scaling patches on the extensor surfaces of the joints of the hands, usually on the joint between the proximal and middle phalanges. There would be room for difference of opinion in some cases, but in the typical case, if it is granted that one can diagnose psoriasis histopathologically, there would seem to be none, and these cases belong in the typical category.

**Acute Disseminated Lupus Erythematosus with Remission Followed by Relapse, with Discoid Lesions.** Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. S. A. WALKER.

DISCUSSION

DR. STEPHEN ROTHMAN: Early in 1946 this girl had a most classic hyperacute lupus erythematosus with a temperature between 104 and 105 F., butterfly erythema and a leukocyte count of 3,000. She remained in a critical condition for six or eight weeks. After administration of huge doses of penicillin (8,000,000 units daily for three days) her condition did not seem to improve, but she lived. I never saw a patient recover from this type of hyperacute lupus erythematosus. Subsequently, roentgen ray castration was carried out with a dose which was thought to be a permanent sterilization dose. European roentgenologists have

expressed the belief that there is a safe temporary sterilization dose, but this view is not shared in this country. In any case, this girl, after one and one-half years of amenorrhea, during which time she was perfectly well, started to menstruate again regularly. Soon after this occurrence, her present discoid cutaneous lesions appeared. This type of relapse is unusual.

The muscular atrophy was interpreted as a progressive degenerative muscular dystrophy probably independent of lupus erythematosus.

DR. ASHTON L. WELSH, Cincinnati: In Cincinnati we have been using large doses of calcium pantothenate in treatment of all types of lupus erythematosus. In the discoid type it has been valuable. We have 11 patients who have had complete clearing and in whom the lesions are in remission on doses up to 2,000 mg. of calcium pantothenate daily. In cases of the acute disseminated types there has not been a response. In some cases of the subacute disseminated types very little change has been shown. In the discoid type, both chronic and disseminate, improvement has been shown.

DR. THEODORE CORNBLEET: The patient complained a good deal of weakness. She has difficulty in raising her arms and in getting about. It may be worth while to make a biospy of muscle tissue to rule out the possibility of dermatomyositis.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: I am not optimistic about any treatment that will benefit lupus erythematosus. In this case, the patient acquired discoid lesions after the disseminated phase of the disease had passed. This is a reverse of the usual sequence; patients who have discoid lesions may show a generalization of these lesions, or they may present the systemic reactions of acute disseminated lupus erythematosus with fatal termination.

NOTE (Feb. 16, 1949).—The disease assumed characteristic signs of myositis, which was confirmed histologically.

**A Case for Diagnosis (Incontinentia Pigmenti of Bloch and Sulzberger? Nevus Pigmentosus et Reticularis with Hyperkeratosis?).** Presented by DR. S. J. ZAKON and (by invitation) DR. I. EIRINBERG, Northwestern University Medical School.

L. G., 3 months of age, was first seen in the Dermatology Clinic, Northwestern University Medical School, on Jan. 12, 1949. When the child was 3 days old her physician noted a papulovesicular eruption on the extensor and flexor surfaces of the arm and legs which gradually became generalized. Because of this feeding with breast milk was discontinued and the child was given mull-soy® (hypoallergenic soy preparation) and local therapy, with some improvement in the condition. The eruption gradually changed until it assumed its present character. Two weeks ago the mother noted hyperkeratotic patches developing on the fingers and toes.

The mother is 21 years old and in good health. This is her second child, and the pregnancy was normal throughout except for considerable pruritus, edema of the ankles and several infections of the upper respiratory tract. Her first child is 2 years old and normal; however, the mother states that the child has a pigmented lesion on the chest. The father is 26 years old and in good health.

On examination L. G. is seen to have a moderately scaly seborrhea of the scalp. The face, chest and abdomen are clear. On the extensor and flexor surfaces of the arms and legs there is a peculiar light to medium brown reticular pigmentation together with an erythematous papular and papulovesicular eruption, some areas of which show crusting. Considerable exfoliation over the palms and soles is present. On the dorsa and sides of the fingers are numerous linear hyperkeratotic lesions.

No associated ectodermal defects have been found thus far, nor can a history of ectodermal defects be elicited on either the maternal or the paternal sides of the family. Biopsy of the lesions and ophthalmoscopic examination will be done.

DISCUSSION

DR. M. R. CARO: I think this is a case of systematized nevus very early in the stage of its development. About eight or ten years ago I saw an identical condition in a baby at the age of 2 or 3 days. The infant had a generalized vesicular eruption. In the next few days the vesicles dried gradually and were replaced by streaks of pigmented and nonpigmented verrucous lesions. Dr. Senear and Dr. Oliver saw the case in consultation when the baby was 2 or 3 months old. There were then thick hyperkeratotic masses, especially on the hand and the feet and over the bony prominences. We thought that the condition was an epidermal nevus. I saw the baby after a year. The keratotic masses had fallen off, leaving very little atrophy. When the child was 3 or 4 years old there were a few whorl-like streaks of pigmented nevus on the abdomen. Most of the lesions had disappeared. In this case the same course of events is apparently occurring and the lesions will in time no doubt develop into typical systematized nevi.

DR. A. W. STILLIANS: I saw the baby when she was only about a week or so old. The picture was very much like that described by Dr. Caro—numerous small vesicles confluent on the inner side of the leg, no pustules, no elevation of temperature, little redness and no signs of any discomfort.

**A Case for Diagnosis (Hodgkin's Disease? Verrucous Lesion?).** Presented by DR. CLINTON W. LANE, St. Louis.

D. A. T., a man aged 52, has had his eruption for thirty years. In 1919, while he was in the Army, three papular lesions appeared on the left arm. Similar lesions gradually appeared elsewhere, and in three years most of the skin surface was involved. The eruption has been present constantly since its onset, although some lesions disappear, with resultant scar formation. Itching is of mild character, and except for the appearance of the eruption the condition does not bother the patient. His general health has always been excellent, but in 1912 a "spot" on the lung was reported by the family physician.

On examination the patient is observed to be a well developed, well nourished, healthy-looking person. An eruption extensively involves the trunk and extremities, but the head and neck have fewer lesions. The genitalia and mucous membranes show no eruption. The primary lesions are firm, bright red papules 2 mm. in diameter, most of which increase in size to form nodules 4 to 5 mm. in diameter. The older papules and nodules have a central necrotic area and are covered with dry crusts and scales. Some lesions, particularly on the legs, are verrucous and button-like and attain a size of 9 mm. in diameter. The lesions regress, leaving red spots, although some become smaller and paler, with retention of outline. The final stage is a white, atrophic scar.

The results of three examinations of the blood are reported: March 15, 1947—erythrocytes, 3,850,000; hemoglobin, 78 per cent, and leukocytes, 8,700, with 64 per cent polymorphonuclear cells, 2 per cent stab cells, 28 per cent lymphocytes and 2 per cent eosinophils; Feb. 11, 1948—erythrocytes, 4,190,000; hemoglobin, 90 per cent, and leukocytes, 7,400, with 64 polymorphonuclear cells, 36 per cent lymphocytes and 10 per cent eosinophils; Nov. 2, 1948—erythrocytes, 4,680,000; hemoglobin, 89 per cent, and leukocytes, 15,600, with 62 per cent polymorphonuclear cells, 2 per cent stab cells, 33 per cent lymphocytes and 7 per cent eosinophils.

The examination of bone marrow showed the following observations: Grossly the marrow appeared hyperplastic. Microscopically there was active myelopoiesis

with a slight increase of the myeloid cells in relation to the erythroid cells. Maturation of the myeloid cells was normal, and no abnormal forms were found; however, there was a pronounced increase in the eosinophilic elements of this type of cell. Maturation of the red cell elements was within normal limits.

The urine was normal, and the Kahn reaction was negative. A roentgenogram of the chest showed a primary tuberculous complex in the left lung, aside from which there was no evidence of pulmonary disease. The tuberculin patch test gave negative results.

Biopsy was made of specimens of a recent and of an old lesion. The sections of the recent lesion were studied by Dr. Hamilton Montgomery of the Mayo Clinic, and the following is an excerpt from his letter concerning them: "Broders expressed the opinion that the new lesion was inflammatory and stated the belief that the large cells were so-called endothelial leukocytes. I could see no evidence of malignant change. For the most part, these large cells appeared to me like endothelial leukocytes or monocytes. A few of them, however, had a very deeply staining nucleus and nucleolus with increase in ratio of the nucleolus to the cytoplasm suggestive of transformation toward a malignant type of cell and resembling somewhat mononucleated forms of the Dorothy Reed or Sternberg cells of Hodgkin's disease."

The old lesion was diagnosed as verruca of undetermined type.

The report on biopsy as made by Dr. John Frerichs of Barnard Skin and Cancer Hospital was as follows: "Microscopic examination of the slides of the recent lesion showed a peculiar infiltration of the upper portion of the cutis and the midcutis with mononuclear cells, some of which were very large, and a fair sprinkling of polymorphonuclear cells. Some of the unusual large cells had prominent nucleoli, and others did not. Mitoses were seen occasionally among them. The nuclei were round to horseshoe shaped and often stained heavily. Cytoplasm was abundant and red to reddish purple. Some vessels showed thickening of the wall and prominence of the lining endothelium."

The slides of the old lesion showed a benign verrucous lesion.

New lesions have continued to develop, to progress to larger verrucous lesions and to result in new scars for the period of observation, fourteen months. Treatment has had no effect and has consisted of the following: the administration of penicillin, 3,000,000 units, and sulfapyridine; injections of foreign protein; the administration of bismuth sodium triglycollamate ("bistrimate"), vitamins A, D and E and sodium paraaminobenzoic acid, and topical applications of numerous preparations.

Prior to observation the patient had received roentgen ray therapy over a period of eight months and had ingested potassium arsenite (Fowler's) solution for seven months.

### DISCUSSION

DR. H. E. MICHELSON, Minneapolis: It is presumptuous to try to make a diagnosis of the condition after this patient has been observed so carefully for so long a time, but some of the facts are interesting. The man has had the condition for thirty years; therefore, it is obvious that it is not serious. It has not affected his general health. He also has no local adenitis. The evolution of each lesion is from a pustule to a scar. Each lesion seems to run its course independent of the others. All the drugs that are used against pus infections have been ineffective. I believe this is a case of chronic folliculitis in which the soil or terrain plays the important role. It is to be likened unto acne conglobata as compared with acne vulgaris.

As far as the sections were concerned, there were numerous odd-looking cells, but one must realize that in so chronic an inflammation there is always a tendency

for the picture to resemble that of lymphoblastoma. Sulfur baths might be tried. They are a good form of therapy in similar conditions.

DR. UDO J. WILE, Ann Arbor, Mich.: I wonder whether one might not consider this a very unusual example of pityriasis lichenoides et varioliformis. I do not know that any type of folliculitis would leave as many of this sort of varioliform-like scars as this man had. To me this did not look like a folliculitis. While the entity of pityriasis lichenoides et varioliformis is a very unusual one, nevertheless it seems to me that this case had some of the characteristics of this syndrome.

**Case for Diagnosis (Senear-Usher Pemphigus?).** Presented by DR. S. R. MERCER, Ft. Wayne, Ind. (by invitation).

D. F. B., a man aged 47, had had an eruption for thirty-two years. It first appeared on the back and a short time later on the chest. Pruritus was rather severe. After being ill in bed at home for several months he was admitted to the Royal Infirmary, Edinburgh, Scotland. At that time the "crusts and scabs" were on the chest, the back and the head. Various ointments were tried, and arsenic was given internally. After nine months of hospitalization the patient was discharged as showing improvement.

For a number of years he was a clinic patient at the Infirmary under the supervision of Dr. Fred Gardner. There then followed a series of admissions and dismissals from the same hospital. The patient states that he was better after each admission but notes that the new skin always seemed to be "very thin and filmy" and that the progress made in the summer was usually lost in the winter. For a number of years "my skin all over became very wet and soggy, and when it dried up it became very dry." He had to use an ointment constantly in order to be comfortable.

Up to about 1945 the usual treatment used was soaks of 0.5 per cent silver nitrate solution, application of crude coal tar ointment and ichthaminol (ichthyol®) paste, besides a bismuth preparation ointment, and the internal administration of an arsenic preparation. In the spring of 1945, while he was a patient at the Royal Infirmary, he became very seriously ill. The head, arms and legs suddenly became covered with pustules. At that time he was given penicillin injections every four hours as well as some "septic drugs" internally. The serious illness lasted about a month. From the turning point of that particular bout he noticed that his skin "looked better in a new way" and that it did not have the acute inflammation that had been more or less present during all the years of his sickness. He showed gradual improvement, gained strength and was discharged from the hospital in 1945.

In March 1948 he came to the United States. During the four or five days that he was on board ship there was a very sudden and severe flare-up of his skin condition. At the time I first saw him he had a mass of bullae fairly generalized. There was a Nikolsky sign and low grade fever. The patient did not appear very ill; however, penicillin in oil was administered, and baths of potassium permanganate and applications of 2 per cent ammoniated mercury ointment were used. In very short order his condition became the same as it is at present.

**Pemphigus Vulgaris: Remission After Treatment with Aureomycin.** Presented by DR. F. E. SENEAR and STAFF.

DISCUSSION OF CASES OF PEMPHIGUS

DR. HERBERT RATTNER: I thought that Dr. Mercer's patient had pemphigus foliaceus rather than erythematoid benign pemphigus. There was not the dis-

tribution on the batwing area of the face or on the central portions of the chest and back to warrant the diagnosis of Senear-Usher syndrome.

In the second patient there was a striking remission after treatment with aureomycin. One should regard any new treatment for pemphigus, however, much as Dr. Brunsting regards new treatments for lupus erythematosus. So many things seem to effect remissions for a time. I recently treated a patient with pemphigus with roentgen rays to the liver and spleen. There followed a striking remission. But there was a recurrence of the pemphigus in three months which did not respond to similar treatment. Roentgen rays were used because the patient had failed to respond to treatment with the usual measures, such as administration of acetarsone, blood transfusion, the Davis treatment and administration of vitamins. Finally we administered polymixin, also to no avail.

DR. STEPHEN ROTHMAN: A patient with pemphigus under my observation did not respond at all to treatment with aureomycin, although he was given maximal dosage for eight days.

In Dr. Mercer's case I should like to consider the diagnosis of dermatitis herpetiformis. This man had an itching bullous disease for thirty-two years. Even if the Senear-Usher syndrome is a relatively benign type of pemphigus, I do not think it ever lasts that long.

DR. H. E. MICHELSON, Minneapolis: My associates and I have treated 2 patients with pemphigus vulgaris with aureomycin without any effect. Both died.

DR. PAUL A. O'LEARY, Rochester, Minn.: There are two points in regard to this case that I should like to discuss. First is the possibility that this patient has a bullous type of Darier's disease rather than a manifestation of pemphigus. The patient informed me that in the summer his condition was materially improved, a point that adds to the possibility of its being Darier's disease rather than pemphigus.

The second point is that in our experience with aureomycin a sterilization of the gastrointestinal tract, which may result in the development of an avitaminosis, frequently occurs. Accordingly, we have found it necessary to supplement the use of aureomycin with the liberal administration of vitamins, especially the vitamin B complex.

DR. FRANCIS E. SENEAR: With regard to the young woman I should like to say at once that we specifically did not have any feeling that aureomycin was necessarily responsible for the remission because remissions occur spontaneously in pemphigus. The effect in this case was very dramatic, but we have had experience with various forms of arsenical therapy and with treatment with sulfonamides and penicillin after which excellent results have been seen and reported; remissions occurred quickly, but on recurrence the same therapy was not effective. We are not at all optimistic about the effect of aureomycin in pemphigus.

This patient was interesting from another standpoint. She acquired the first lesions on the scalp, apparently the primary lesions, about eleven months ago in February and was seen by at least three of our colleagues. When she came to us last June she had a classic picture of pemphigus erythematosus, with lesions on the face and typical hyperkeratolytic lesions on the face and back. She then acquired several months ago, in November, typical pemphigus vulgaris, as happens frequently in these cases.

With regard to Dr. Mercer's patient, the question is whether or not the disease is pemphigus erythematodes. The picture certainly is not classic. The English school, however, seems to have had a considerable experience with cases of that type which originally were of the erythematosus type and developed into the foliaceus type, so much so that Gray expressed the opinion that the erythematosus

type is a variant of pemphigus foliaceus. In our experience most of these cases terminate as pemphigus vulgaris. Some of them start out as pemphigus foliaceus and develop into the erythematous type. Dr. Mercer's patient has a definite Nikolsky sign demonstrated within the lesion. He told me that earlier it could be demonstrated generally. On the lower portion of the back there were a good many hyperkeratotic lesions which would fit in very well with the picture for pemphigus erythematosus. I have crystallized my feeling in regard to pemphigus erythematosus to the point that I think this condition is unquestionably a form of pemphigus. In Dr. Mercer's patient the picture is more that of pemphigus vulgaris. Many of these cases eventuate as this or as pemphigus foliaceus. As to the duration, I do not think that is important. The first patient we had and

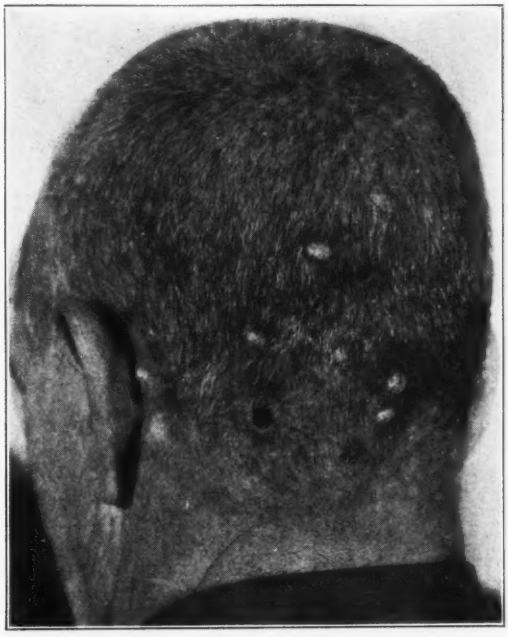

Fig. 1.—A case for diagnosis (turban-like tumors of the scalp with a histologic picture resembling that of lymphoblastoma).

the one whose case we used as the basis of our report had had the disease for many years. Dr. Mitchell and Dr. Ormsby demonstrated 2 cases in which the disorder had also lasted for many years.

**A Case for Diagnosis (Turban-like Tumors of the Scalp with a Histologic Picture Resembling That of Lymphoblastoma).** Presented by Dr. S. J. Zakon and (by invitation) Dr. I. Eirinberg, Northwestern University Medical School.

DISCUSSION

Dr. John F. Madden, St. Paul: I think this is dermatitis papillaris capillitii, an eruption described by Dr. Robert Barney while on Dr. Wile's service. There

is folliculitis, scarring and keloid formation in this case. I think that the nodules in the neck are enlarged lymph nodes draining the infection in the scalp.

DR. S. J. ZAKON: When we first examined this patient we thought we were dealing with early turban-like tumors secondary to metastases of some visceral carcinoma, such as Dr. F. Ronchese reported a few years ago. When the sections came through we were surprised. We saw the lymphoblastic infiltrate. Then the results of examination of the blood showed 11 per cent eosinophils in a total white blood cell count of only 8,000. In the material taken on sternal puncture there were 16 per cent eosinophils, an observation which was definitely pathologic.

We did not consider a diagnosis of dermatitis papillaris capillitii. The histologic picture is not that of a banal inflammatory reaction. I showed the sections

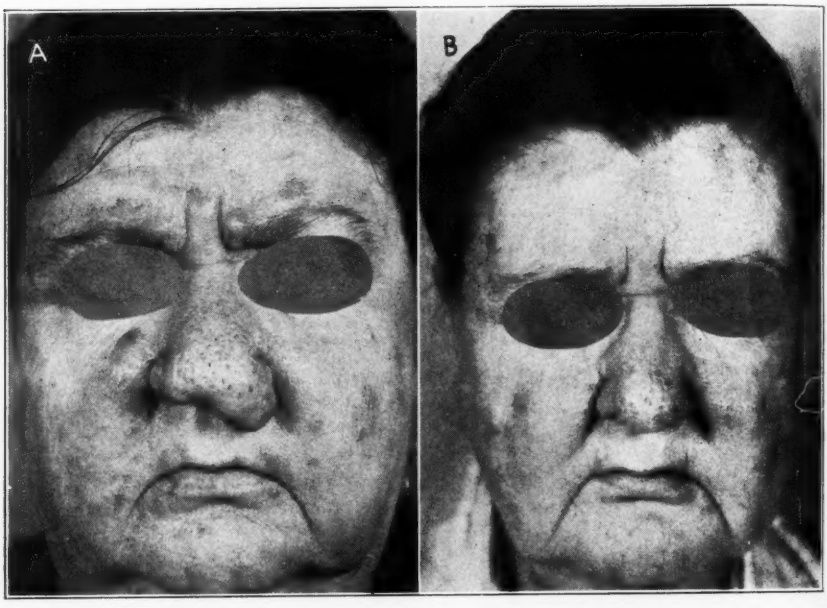


Fig. 2.—Rhinophyma and acne rosacea. *A*, rhinophyma before treatment; *B*, rhinophyma after treatment with electrosection current.

to a number of competent general pathologists, and their diagnoses varied from mycosis fungoides to other members of the lymphoblastoma group.

**Extensive Xanthomatosis with Involvement of Cornea.** Presented by DR. THEODORE CORNBLEET and (by invitation) DR. D. COHEN and DR. D. MUSGRAVE.

**Pseudoatrophoderma Colli of Neck, Chest and Abdomen.** Presented by DR. MICHAEL H. EBERT and (by invitation) DR. VERA LEAF and DR. D. MUSGRAVE.

**Lichen Striatus in a Seven Month Old Boy.** Presented by DR. D. V. OMENS and (by invitation) HAROLD OMENS and DR. D. MUSGRAVE.

**A Case for Diagnosis (Malignant Melanoma of the Toe?).** Presented by DR. JAMES R. WEBSTER and S. M. BLUEFARB and (by invitation) DR. D. MUSGRAVE.

**Calcinosis and Leg Ulcers in a Patient Who Was Given the Diagnosis of Acute Disseminated Lupus Erythematosus and Who Now Has a Psychosis.** Presented by DR. THEODORE CORNBLEET and (by invitation) DR. H. SCHORR and DR. D. MUSGRAVE.

**Generalized Progressive Scleroderma.** Presented by DR. D. V. OMENS and (by invitation) DR. HAROLD OMENS and DR. D. MUSGRAVE.

**Seborrheic Dermatitis: Moniliasis? Dermatitis Medicamentosa (Potassium Iodide).** Presented by DR. THEODORE CORNBLEET and (by invitation) DR. D. Cohen and DR. S. Barsky.

**Kaposi's Sarcoma of the Legs, Forearms and Hands.** Presented by DR. THEODORE CORNBLEET and (by invitation) DR. D. COHEN and DR. S. BARSKY.

**A Case for Diagnosis (Erythema Toxicum Perstans? Dermatitis Herpetiformis?).** Presented by DR. D. V. OMENS and (by invitation) DR. HAROLD OMENS and DR. S. BARSKY.

**A Case for Diagnosis (Lupus Erythematosus? Lichen Planus of the Scalp?).** Presented by DR. F. J. KENDRICK, Gary, Ind. (by invitation).

**Xeroderma Pigmentosum in a Six Year Old Girl with Tumors (Epitheliomas?) On the Face.** Presented by DR. SENEAR and STAFF

**Necrobiosis Lipoidica with No Evidence of Diabetes.** Presented by DR F. J. KENDRICK, Gary, Ind. (by invitation).

**Necrobiosis Lipoidica Diabeticorum.** Presented by DR. LOUIS RUBIN (by invitation).

**Urticaria Pigmentosa in an Eight Month Old Infant.** Presented by DR. JAMES WEBSTER and (by invitation) DR. FRANCIS HETREED and DR. ALFRED B. FALK.

**Neurodermatitis with Peculiar Papillary Eruption.** Presented by DR. A. W. STILLIANS.

**A Case for Diagnosis (Healed Tertiary Tuberculoid Syphilis?).** Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. S. A. WALKER.

**Darier's Disease, "Forme Fruste."** Presented by DR. E. L. LADEN. (by invitation).

**Rhinophyma and Acne Rosacea, Treated with Electrosection Current.** Presented (by invitation) by DR. W. A. ROSENBERG, DR. I. M. FELSHER and DR. A. H. SLEPYAN.

**Parapsoriasis Guttata (Pityriasis Lichenoides Chronica).** Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. A. L. LORINCZ.

**A Case for Diagnosis (Seborrheic Dermatitis? Dermatomyositis?).** Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. F. V. HAUSER.

**Lichen Sclerosus et Atrophicus.** Presented by DR. EARLE R. PACE.

**Pili Torti.** Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. FREDERICK V. HAUSER.

**Carl W. Laymon, M.D., *President***

**James R. Webster, M.D., *Secretary***

***Feb. 16, 1949***

**Atrophoderma with Telangiectasia.** Presented by DR. OLIVER S. ORMSBY.

A Polish woman aged 53, presents a disorder of forty-three years' duration. The case was fully described in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY (**18**:306 [Aug.] 1928; **20**:388 [Sept.] 1929; **21**:606 [April] 1930). A brief abstract follows.

The first cutaneous change noted was a rough chapped condition which began on the knees when the patient was 10 years old. It gradually progressed upward, involving the thighs and trunk in three years. During the next two years the upper extremities were involved; nodular lesions appeared in various areas during the following five years. As the disease progressed, redness, scaling and wrinkling occurred. The face was the last to become involved, about thirty-eight years after the onset. At this time the eruption was generalized and consisted of wrinkled, scaling, telangiectatic and atrophic patches of varying dimensions. In addition, there were thickened, scale-covered pale red patches and superficial nodules. Over the breasts, on the external and internal surfaces of the arms and over the hips and buttocks were large patches in which the skin was wrinkled, atrophic and telangiectatic. In these areas red (telangiectatic) lines surrounded rhomboidal white areas, giving a striking appearance. The white areas measured 3 by 5 mm., each being encircled by a network of vessels. The thickened scaling patches were situated chiefly on the abdomen and the thighs. On one thigh near the knee were two rings of superficial flat, pale red nodules. Pale red scaling patches varying in size from that of a pea to that of a bean were present on the face, and moderate scaling was present in the scalp. Pruritus and burning sensations had been complained of during the entire time the patient had been under observation, but there had never been any visible evidence of scratching.

Histologic examination of a section removed from a patch near the axilla posteriorly showed a dense, sharply defined, cellular infiltration of the upper third of the corium, composed chiefly of lymphocytes; appreciably dilated blood vessels; destruction of the elastic tissue and of some of the collagenous tissue, chiefly at

the site of the cellular infiltration, and obliteration of the rete pegs. The epidermis was thinned in some areas (Finnerud). Histologic examination of a nodule removed from near the knee showed parakeratosis with collections of serum in the horny layer, acanthosis of the psoriasiform type and partial absence of the stratum granulosum. The corium was edematous; its vessels were dilated in the subpapillary portion, and there was a fairly dense, rather sharply defined perivascular cellular infiltration.

At the time of presentation, the eruption on the face has cleared up. The general scaling and wrinkling are reduced; the telangiectasia remains unchanged, and the atrophy is slightly increased.

Tests of the blood and examination for changes in the glands of internal secretion revealed no demonstrable pathologic condition. Thyroid therapy seemed to be of some value.

On May 11, 1948, a tumor on the left side of the neck was removed surgically. The clinical diagnosis of this tumor was Hodgkin's disease. The histologic report follows:

"There were numerous areas of fibrosis with broad irregular bands subdividing the structure of the lymph nodes. In many areas the lymphatic tissue contained well developed lymph follicles with histiocytic germinal centers. In these areas the sinuses were often essentially normal or were dilated moderately and contained a few eosinophils and many larger cells which resembled swollen reticulum cells.

"In other areas the normal structure of the lymph nodes was missing and one of two types of changes might be seen. In a few of these areas there were large numbers of eosinophils, plasma cells and a few leukocytes. In addition, there were many larger single-nucleated cells of the reticulum type. The other type of change was seen in a few areas and consisted of small solid masses of large cells of the reticulum type which appeared to be in sinuses, were quite anaplastic, had a few mitoses and were infiltrated by many eosinophils."

After the surgical removal of the glands in May 1948, the cutaneous symptoms largely cleared up, leaving a brownish reticulated appearance.

DISCUSSION

DR. HAMILTON MONTGOMERY, Rochester, Minn.: This is a very unusual case in that Dr. Ormsby has had the opportunity of observing this patient for more than twenty years and in that within the last year the patient has acquired Hodgkin's disease, as observed on biopsy of a lymph node. Dr. Ormsby showed me the slides this morning of the original cutaneous biopsy specimen taken in 1927, and I made a diagnosis of acrodermatitis atrophicans chronica. In 1927, Dr. Finnerud, according to the office notes, had made a diagnosis of idiopathic atrophy of the Herxheimer type, which means the same thing as acrodermatitis atrophicans chronica. One usually associates this disease with involvement of the extremities, but I have seen patients in whom there was extensive generalized involvement and also patients in whom the acrodermatitis was preceded by a generalized erythroderma (ARCH. DERMAT. & SYPH. **51**:32-46 [Jan.] 1945). I think this case falls into the last-mentioned group.

DR. MAURICE OPPENHEIM:† This is a very interesting case because it has been observed over such a long period. My first impression was of dermatitis atrophicans chronica. There are no hyperkeratotic areas, but only hyperpigmentation and telangiectasis besides the atrophy. I believe the correct diagnosis here is atrophic idiopathic dermatitis with pigmentation and telangiectasis.

DR. OLIVER S. ORMSBY: I want to apologize for presenting such an old case, but on account of what happened during the last year I thought it was worth

† Dr. Oppenheim died on Oct. 27, 1949.

while to show the patient again. Up until a year ago the condition kept getting gradually worse. The patient had a generalized eruption consisting of exfoliative dermatitis with atrophy. An enormous amount of telangiectasia covered the breasts, back and arms, and there was some on the lower extremities. In addition the patient had a large number of patches varying from palm size to larger. These appeared particularly on the arms and legs, but some were seen on the body. These patches were psoriasiform and gave much trouble. I have had the patient under observation for twenty-two years. Last January her condition was about as I have just described it and she was not at all strong. She then manifested growth of a group of glands on the side of the neck below the jaw. Her family physician excised those glands, and in about two months the skin entirely cleared up. All the telangiectasia disappeared. All the scaling and the atrophy did not go completely, but all activity of the disease disappeared after that operation. I cannot account for the occurrence. The operative procedure showed that this patient had acquired Hodgkin's disease. That had nothing whatever to do with her previous trouble. I cannot account for the disease's clearing up as it has unless it is that the profound effect of Hodgkin's disease on the general condition has removed the skin symptoms. That happens once in a while. Patients may have a very serious skin disease and have a disease of another kind, particularly a febrile disease, and skin symptoms even of leprosy will clear up but may later recur. In this case skin symptoms have not recurred, but the patient is not strong. It is a most extraordinary thing to see her today and to remember how she looked even a year ago.

**Periungual Fibromatous Tumors and Subungual Hyperkeratosis.** Presented by DR. F. J. KENDRICK, Gary, Ind. (by invitation).

Mrs. I. M., a white woman aged 26, has had periungual growths about the edges of about half her toe nails and finger nails of some ten years' duration. Some have been removed with cautery in times past, always with regrowth.

In the past two or three years subungual, hard, horny, brushlike growths have appeared beneath many of her nails. These growths appear to originate from about the center of the bed, elevate the nail and push out beyond the distal edge of the nail. Scrapings from these horny growths have been examined a dozen times, but no fungi have been found.

Results of serologic examination were negative. Suggestions as to therapy would be welcomed.

**Juvenile Elastoma? Pseudoxanthoma Elasticum?** Presented by DR. JAMES H. MITCHELL and (by invitation) DR. H. N. SANFORD and J. W. GRAFFIN.

M. M., a white girl born on Oct. 5, 1948, when two months of age acquired skin lesions on the forehead. This eruption had been preceded continuously by five weeks of severe diarrhea and vomiting, accompanied by one episode of circulatory collapse. Dr. H. N. Sanford hospitalized the child twice at the Presbyterian Hospital, and after ten weeks of chemotherapy, parenteral administration of fluids and dietary management, the child made a complete recovery. Green-producing streptococci were repeatedly recovered from the throat and stool cultures.

During December, at a time when the gastroenteritis was clinically improving, the child acquired a yellowish "xanthoma-like" eruption limited to the left temporoparietal and retroauricular areas and extending slightly within the hair line. The lesions consisted of firm yellowish nodules, some discrete and others coalescing to form plaques, the nature of which is depicted by a color slide taken on December 28. In a telephone conversation the father stated that the character of the lesions

had changed to "red, oozing sores with crusting." The family history concerning skin and congenital anomalies is noncontributory, and the child has no other physical abnormalities.

The complete blood count varied during hospitalization, the erythrocytes from 3,600,000 to 4,400,000 per cubic millimeter, the leukocytes from 10,200 to 12,800 per cubic millimeter and the hemoglobin from 10.0 to 13.8 Gm. per hundred cubic centimeters. One catheterized specimen of urine was normal. One examination of the spinal fluid revealed no evidence of syphilis, tuberculosis or bacterial organisms; however, there were 50 white blood cells per cubic millimeter, the protein content was 100 mg. per hundred cubic centimeters (30-70), and the amount of sugar was 55 mg per hundred cubic centimeters (40-60). The total cholesterol was 102 mg. per hundred cubic centimeters (125-360).

On Jan. 6, 1949, a yellowish nodule was removed from the scalp, and histologic sections were prepared with hematoxylin and eosin and elastic tissue stains. Microscopic examination revealed an essentially normal epidermis. The subepidermal layer of the corium appeared normal, but throughout the remainder of the dermis there was a decidedly abnormal arrangement and degeneration of collagen and elastic tissue. There was a mild infiltration by lymphocytes, eosinophils and polymorphonuclear cells; giant, xanthoma and nevus cells were absent. The blood vessels were relatively sparse and showed nothing unusual. There was a considerable amount of calcium present in the dermis, and there were numerous hair shafts and smooth muscle elements extending into the subcutaneous tissue.

**Urticaria Pigmentosa.** Presented by Dr. David V. Omens and (by invitation) Dr. Harold Omens and Dr. D. Musgrave

**Psoriasis? Forme Fruste of von Recklinghausen's Disease?** Presented by Dr. Michael H. Ebert and (by invitation) Dr. Vera Leaf and Dr. S. Barsky.

DISCUSSION OF PRECEDING FIVE CASES

Dr. Stephen Rothman: My impression of Dr. Kendrick's case was that the lesions are filiform veruccae around the nail and close to the free end of the nail.

Dr. Mitchell's case impressed me as being one of localized nevoxanthoendothelioma. If this diagnosis is correct, the lesion will disappear spontaneously.

Dr. A. L. Welsh, Cincinnati: Dr. Kendrick's case presents an incomplete Bourneville's syndrome including subungual fibromas and adenoma sebaceum. The patient has beginning hypertrophy of the interdental papillae, which is part of the syndrome, but does not have filiform projections on the tongue. This interdental enlargement is moderate, but it is definite. This patient did not seem to have tuberous sclerosis, another part of the syndrome.

Dr. F. W. Lynch, St. Paul: I agree with Dr. Welch that Dr. Kendrick's case deserves the title of the entire syndrome even though the number of demonstrated features is small. Among the less frequently recognized features in this disorder are the multiple retinal cysts or tumors, which evidently are present much more frequently than is generally recognized. I think they may be worth searching for in this case.

With reference to Dr. Mitchell's case I had somewhat the impression that Dr. Rothman held. The sections seem to show degenerative changes in the cutis suggesting that the crusting and surface changes may be secondary to the deeper ones. Similar changes are sometimes seen in the cutis in cases of nevoxanthoendothelioma.

I wonder whether the term of von Recklinghausen's disease is justified in Dr. Ebert's case. It seems to me that one must be hesitant about applying this diagnosis when only pigmentary changes are seen. In this instance the large number of lesions, their small size, the systematic arrangement which is chiefly unilateral and the absence of other demonstrable changes would lead me to regard the condition as a pigmented nevus. The pigmented macules of von Recklinghausen's disease usually tend to be somewhat lighter in color and less regular in their outline.

**A Case for Diagnosis (Dermatomyositis? Lupus Erythematosus?).** Presented by Dr. Adolph Rostenberg Jr. and (by invitation) Captain R. A. Brown, Battle Creek, Mich.

**A Case of Disseminated Lupus Erythematosus in Remission.** Presented by Dr. James H. Mitchell and (by invitation) Dr. J. W. Graffin.

**Acute Disseminated Lupus Erythematosus.** Presented by Dr. Theodore Cornbleet and (by invitation) Dr. H. Schorr and Dr. D. Musgrave.

DISCUSSION OF PRECEDING THREE CASES

Dr. Hamilton Montgomery, Rochester, Minn.: The question of the relation between dermatomyositis and disseminated lupus erythematosus has been brought up in the past and will continue to be until we know the cause of both conditions.

I believe that in the greatest majority of cases one can distinguish between disseminated lupus erythematosus and dermatomyositis. Leukopenia, fever and disturbance in the albumin-globulin ratio, together with other systemic manifestations that are associated with disseminated lupus erythematosus, are usually not found in dermatomyositis. In acute phases of disseminated lupus erythematosus the so-called L. E. cell can be demonstrated in sternal aspirations, and the L. E. cell as described by Hargraves is not present in patients with dermatomyositis. I think case 12 is one of lupus erythematosus and not dermatomyositis even though there is muscle weakness. In dermatomyositis the cutaneous lesions may have the same distribution that is seen in disseminated lupus erythematosus, including involvement of the face and V of the neck, but histologically there is only toxic dermatitis and one does not see the characteristic changes of lupus erythematosus.

Dr. Carl Laymon, Minneapolis: Last month at a meeting of the Minnesota Dermatological Society in Minneapolis the value of biopsies of muscle was discussed. The men who entered the discussion were of the opinion that this procedure has been overrated both for lupus erythematosus and for dermatomyositis.

Dr. Adolph Rostenberg Jr.: I first saw my patient one month ago, and I could not make up my mind as to the diagnosis. Originally I thought of poikiloderma vasculare atrophicans, but today I think the condition looks more like lupus erythematosus. Dr. Cawley and Dr. Curtis saw the patient at first and thought the condition was lupus erythematosus. The case is of interest from the pathologic point of view. Slides from this case were shown to various experts, and the diagnoses ranged from acute lichen planus to localized myxedema. We had only one biopsy of muscle tissue, and that did not reveal anything of significance. It was of interest, however, that the skin overlying the area from which the muscle specimen was taken was grossly normal. Yet histologically the changes of lupus erythematosus were evident.

Dr. Hamilton Montgomery, Rochester, Minn.: There are borderline cases between dermatomyositis and lupus erythematosus that may require prolonged observation. My associates and I have 1 patient who now has been under obser-

vation for five years concerning whom we have yet to arrive at a definite diagnosis between the two diseases. There was 1 patient with disseminated lupus erythematosus who clinically had no evidence of muscle weakness, at least not enough for the clinician to make a note on the record, but in whom at postmortem examination diaphragmatic and pectoralis muscles revealed all the changes that are seen in dermatomyositis. As Dr. Madden (personal communication) has emphasized, muscle biopsies have been taken in too few cases of disseminated lupus erythematosus. I still believe that lupus erythematosus and dermatomyositis are two different conditions.

DR. J. W. GRAFFIN: In Dr. Mitchell's and my case the condition was in remission and at one time in the course she appeared in the terminal stage for several weeks. The blood count went down to 1,400 white cells, and at that time the patient was given penicillin and blood; she made a gradual clinical recovery. However, if she had been given spray irradiation or roentgen ray castration, these measures would have been given credit for the remission. We presented the case to illustrate the point that the patient made a clinical recovery on treatment with penicillin and supportive measures only. She has had spontaneous amenorrhea since the age of 31 years.

DR. STEPHEN ROTHMAN: I do not believe that the administration of penicillin can be called just a "supportive measure." It is not decided whether or not penicillin has an effect in treatment of acute lupus erythematosus. Apparently small doses have no appreciable effect, but certainly huge doses (8,000,000 units daily for three days) profoundly influence the course of the disease and may cause recovery from the acute attack. Thus smaller doses may have some effect, too.

DR. JAMES H. MITCHELL: I should like to agree with Dr. Rothman's statement that penicillin is probably of value. In the last number of *The Medical Clinics of North America* (**33**:79 [Jan.] 1949) Drs. Graffin, Taylor and Hass gave an excellent report of a case which we had in the Rush Skin Clinic and Presbyterian Hospital. The patient came in apparently in the terminal stage, and I wanted to see how much effect penicillin alone would have. She came out of that attack beautifully and subsequently also recovered. There was a recurrence later, and while under treatment with sodium paraaminobenzoate the patient died.

DR. FREDERICK BECKER, Duluth, Minn.: I believe that the reason penicillin occasionally helps in some cases of disseminated lupus erythematosus is that this agent prevents many of the acute infectious diseases from developing in a patient with the lowered resistance that is always present with this disease. The treatment of agranulocytosis is with penicillin, and recently the best therapeutic agent for acute leukemia has been penicillin, as it apparently prevents the patients from acquiring fatal infections and tides them over the acute stage for a period.

DR. STEPHEN ROTHMAN: Most patients with lupus erythematosus have no detectable secondary infection and no septicemia. I know of only 1 case in which streptococci were found in the blood, and this observation was made terminally, just before death. Thus, if penicillin acts at all, it does not act by preventing secondary infection. From huge doses of penicillin lately my associates and I saw fatal activation of the disease in 1 case. Therefore, we recommend this treatment only in cases in which the situation appears to be absolutely hopeless and in which the family realizes the hopelessness of the situation and is willing to take the risk.

Those who believe that castration also should be tried in young females imply that estrogenic hormone is a seriously aggravating factor in the course of this disease. However, nobody has implied that estrogenic hormone is a causative agent.

DR. MAURICE OPPENHEIM: I have discussed 2 cases here of lupus erythematosus acutus disseminatus treated with penicillin also. In 1 there was no exacerbation but in spite of all possible treatment the patient died. He was an 18 year old West Point cadet. In the other case, of a girl of 7 with lupus erythematosus acutus disseminatus, penicillin was used, too, and the patient died. I do not think penicillin has any effect on acute lupus erythematosus disseminatus.

**Leiomyomata Cutis Originating from Arrectores Pilorum Muscles.** Presented by DR. A. L. LORINCZ and DR. R. B. STOUGHTON (by invitation) and DR. STEPHEN ROTHMAN.

**Leiomyoma Cutis.** Presented by DR. T. CORNBLEET and (by invitation) DR. D. COHEN and DR. D. MUSGRAVE.

H. C., a 35 year old Negro woman, states that she first noticed a small black nodule on the inner surface of the left upper part of the thigh about seven years ago. This lesion has gradually enlarged. There are no subjective symptoms.

Over the medial surface of the left upper part of the thigh is found a quarter-sized, deeply pigmented, moderately indurated plaque.

A biopsy specimen is presented.

DISCUSSION OF CASES OF LEIOMYOMA CUTIS

DR. MARCUS CARO: The first case was perfectly typical both clinically and histologically. The clinical picture of the other case, however, was a surprise to me. The section was diagnostic, but the lesion on the thigh did not even suggest to me the diagnosis of leiomyoma cutis.

DR. A. L. WELSH, Cincinnati, Ohio: I should like to suggest a type of therapy for leiomyoma. We used liquid oxygen, applying it with pressure by means of a cotton applicator. We have had 2 patients who responded very well to this type of therapy, the condition eventuating with soft minimal scars.

DR. CHESTER SIDELL, Grand Rapids, Mich.: I have observed a case of extensive leiomyoma of the left arm, shoulder and trunk. In some areas the lesions are so close together that they form plaques. The patient had acute attacks, and my associates and I gave her tetraethyl ammonium bromide with complete relief of symptoms. Then we precipitated an attack with epinephrine and during the attack gave her tetraethylammonium bromide with almost instant relief. It had been suggested to her that sympathectomy be done, but during the past two years she has insisted on continuing with treatment with tetraethylammonium bromide. Her attacks are occurring less frequently. I do not know why, but results of treatment have been dramatic in her case. Before this treatment she made two attempts to take her life, but since the treatment she has felt well.

DR. MARCUS CARO: Has there been any change in the appearance of the lesions?

DR. CHESTER SIDELL, Grand Rapids, Mich.: None whatever.

DR. STEPHEN ROTHMAN: What are the toxic risks?

DR. CHESTER SIDELL, Grand Rapids, Mich.: They exist, but the patient was in such poor condition that we felt the risk was justified. We administer the tetraethylammonium bromide both intravenously and intramuscularly, but the patient gets more relief from intravenous administration.

DR. THEODORE CORNBLEET: My associates and I have used tetraethylammonium (etamon®) and found that a few patients obtain a moderate degree of relief from itching or pain as in herpes zoster. This agent blocks both sympathetic and

parasympathetic ganglions, and we found some limited action too on the peripheral cutaneous nerves. Lately we have been making observations on two drugs (supplied by Parke, Davis & Company) somewhat related in their action but not as yet available commercially. One of them, known as Sy-28, is sympatholytic, and we found it more consistent in relieving painful herpes zoster. The latter drug has the advantage over tetraethylammonium in that it may be taken by mouth and has fewer unpleasant side reactions. If Dr. Sidell would like to try this drug for alleviation of the pain in his patient with leiomyoma cutis, I shall be glad to share my supply with him.

**Lichen Striatus.** Presented by DR. D. V. OMENS and (by invitation) DR. H. OMENS and DR. D. MUSGRAVE.

C. D., a 7 month old Negro boy, was presented a month ago. He is presented again to show the improvement which has taken place.

**Epithelioma Adenoides Cysticum.** Presented by DR. A. W. STILLIANS.

Mrs. McD., a widow aged 66, by occupation a secretary, six months ago noted a red spot on the ridge of her nose, which slowly grew and became scaly. She was first seen by me on Jan. 15, 1949. The lesion just above the center of the nasal ridge was 12 mm. wide and 10 mm. in the line of axis of the body, bright red and moderately elevated, with adherent scales at the center. It was not painful or tender. At the left side there was an extension 5 mm. long and 1 mm. broad. Since then the lesion has slowly enlarged, measuring now 22 mm. across and 12 mm. in the line of axis. The patient states that her nose was injured in infancy. There is no familial history of growths on the face or scalp.

A small biopsy specimen taken January 29 was reported as showing the picture of benign cystic epithelioma, showing horn cysts in the surface epithelium and below it edematous tissue with considerable infiltrate, mostly lymphocytes and many cross sections of round epithelial bodies. These showed at the center concentric layers of keratin; outside of these were cells containing granules of keratohyalin, and outside of these were several layers of epithelial cells. No mitoses were seen.

Blood and urine were normal.

DISCUSSION

DR. CLARK W. FINNERUD: I think an error was made here because the tissue was cut on the bias. Clinically the lesion appeared to me to be lupus erythematosus, and I thought microscopically there was no question about the diagnosis. The specimen is a good illustration of lupus erythematosus of the discoid type with improper cutting of the tissue.

**Epidermolysis Bullosa Simplex (Hereditary).** Presented by DR. LOUIS RUBIN (by invitation).

Miss F. E. B., a 19 year old college student, has suffered from formation of bullae after trauma since birth. This tendency has been less since puberty. Most lesions occur on the hands and feet, but they occur also at sites of pressure from constrictive clothing. Lesions are more frequent in summer and occasionally occur in the mouth after contact with hot foods. On healing they leave pigmentation but no scarring.

Results of a general physical examination were normal. The blood count and results of routine urinalysis were normal; the roentgenogram of the chest showed normal conditions and the reaction in the Kahn test was negative; the

basal metabolic rate was —7. The urine did not contain uroporphyrins I and III and urobilinogen but did contain coproporphyrins and deuteroporphyrins and faint traces of protoporphyrins.

DISCUSSION

DR. FREDERICK SCHMIDT: There was a group of obligate porphyrias which occurred in adults which was studied in Argentina by Dr. Borda; the lesions were localized to the arms, hands and face. They came on suddenly and were characterized clinically by bullae, erosions and pigmentation. Consequently Borda called this syndrome bullous, erosive and pigmented porphyria of adults. I had the good fortune to see several of these cases. Not only were there cutaneous symptoms but also there were pronounced melanosis and hypertrichosis associated with severe intestinal symptoms and liver dysfunction. Another interesting point is that all the cases were precipitated by some sensitizing infection, and there it was chiefly an amebic infection. Borda published his book on the porphyrias in 1945, and he repeatedly mentioned the work of Dr. Brunsting.

DR. ROBERT R. KIERLAND, Rochester, Minn.: Epidermolysis bullosa as presented by this patient is not that associated with porphyria. Porphyria as we know it is associated with increase of uroporphyrin, which is the pathologic porphyrin, rather than coproporphyrin. Dr. Schmidt has discussed an entity which has been described in this country by Brunsting and Mason (Porphyria with Cutaneous Manifestations, *Proc. Staff Meet., Mayo Clin.* **22**:489-494 [Oct. 29] 1947; Porphyria with Epidermolysis Bullosa, *J. A. M. A.* **132**:509-513 [Nov. 2] 1946). We have seen a number of these patients who, besides the cutaneous manifestations of bullous reaction on the exposed surfaces of the body, colloid milia and pigmentation and a positive Nikolsky sign, gave a history of alcoholic bouts and evidence of hepatic dysfunction. Treatment directed toward the hepatic dysfunction produced beneficial results on the skin. We have classified this cutaneous reaction as a pseudoepidermolysis.

DR. A. L. WELSH, Cincinnati: There is another type of this condition, which occurs in children and is known as the Weber-Cockayne syndrome. In this type the lesions occur almost entirely on the palms and soles and have a tendency to flare in the summer and to disappear in winter. In this type, uroporphyrin is present in the urine. The condition tends to disappear spontaneously at the end of puberty. This type is not that just described by Dr. Frederick Schmidt.

DR. STEPHEN ROTHMAN: The eruption of this patient has been present since birth, and the bullae have appeared at pressure points. The family tree indicates simple dominance. Thus there can be no doubt that the case is one of epidermolysis bullosa simplex. Pathologic amounts of coproporphyrin in the urine have been reported in several cases of this entity.

**Biliary Cirrhosis in a Woman with Generalized Xanthomatoses, Spider Nevi—Red Palms, Jaundice and Mild Pruritus.** Presented by DR. F. E. SENEAR and Staff.

**Pseudoxanthoma Elasticum of Neck with Angioid Streaks.** Presented by DR. MICHAEL H. EBERT and (by invitation) DR. ALLEN S. PEARL JR.

**Lupus Vulgaris Successfully Treated with Calciferol.** Presented by DR. MAURICE OPPENHEIM and (by invitation) DR. WILLIAM A. YACULLO.

**Disseminated Lupus Vulgaris with Carcinoma Treated with Calciferol.** Presented by DR. MAURICE OPPENHEIM and (by invitation) DR. WILLIAM A. YACULLO.

**A Case of Lupus Vulgaris Tumidus of the Face Treated with Calciferol.** Presented by DR. MAURICE OPPENHEIM and (by invitation) DR. WILLIAM A. YACULLO.

**Tuberculous Adenitis? Lymphogranuloma Inguinale? Scrofulodema?.** Presented by DR. THEODORE CORNBLEET and (by invitation) DR. D. COHEN and DR. S. BARSKY.

**Scleroderma.** Presented by DR. F. E. SENEAR and Staff.

**Scleroderma.** Presented by DR. THEODORE CORNBLEET and (by invitation) DR. H. SCHORR and DR. S. BARSKY.

**Linear Lichen Planus.** Presented by DR. D. V. OMENS and (by invitation) DR. H. OMENS and DR. D. MUSGRAVE.

**A Case for Diagnosis (Annular Hypertrophic Lichen Planus?).** Presented by Dr. Michael H. Ebert and (by invitation) Dr. Allen S. Pearl Jr.

**Lichen Nitidus in an 8 Year Old Negro Girl.** Presented by Dr. M. Felsher, Dr. A. Slepyan and (by invitation) Dr. S. Steinberg.

**A Case for Diagnosis (Aphthous Erosions?).** Presented by Dr. Maurice Oppenheim and Dr. William A. Yacullo (by invitation).

**A Case for Diagnosis (Atrophic Lichen Planus? Morphea?).** Presented by Dr. Francis E. Senear and Dr. Irene Neuhauser.

**Arsenical Keratoses with Degenerative Changes.** Presented by Dr. F. E. Senear and Staff.

**Lichen Spinulosus.** Presented by Dr. A. M. Buchholz.

**Periarteritis Nodosa (?), Cutaneous Form, Nodular Vasculitis (?) Associated with Hypersensitivity to Iodides.** Presented by Dr. William A. Rosenberg (by invitation).

**Pityriasis Lichenoides (Transition from the Acute Form of Habermann to the Chronic Form of Juliusberg?)? Guttate Psoriasis?** Presented by Dr. Stephen Rothman and (by invitation) Dr. P. L. Beal.

**Extensive Carcinoma Cutis of the Thigh.** Presented by Dr. H. Rattner and (by invitation) Dr. H. Rodin and Dr. D. Musgrave.

**Acquired Leukoderma Occurring after the Use of a Shoe Dye.** Presented by Dr. T. Cornbleet and (by invitation) Dr. D. Cohen and Dr. S. Barsky.

**Chronic Nutritional Dermatitis of the Legs.** Presented by Dr. T. Cornbleet and (by invitation) Dr. D. Cohen and Dr. S. Barsky.

**A Case for Diagnosis: Ulcer of Buttock.** Presented by Dr. M. Ebert and (by invitation) Dr. A. Pearl and Dr. S. Barsky.

**A Case for Diagnosis: Grouped Follicular Papules in a Negro.** Presented by Dr. M. Ebert and (by invitation) Dr. Vera Leaf and Dr. D. Musgrave.

**A Case for Diagnosis (Leukemic Nodules of Leg?).** Presented by Dr. D. Omens and (by invitation) Dr. H. Omens and Dr. D. Musgrave.

**Fox-Fordyce Disease and Verruca of Genitalia.** Presented by Dr. H. Rattner and (by invitation) Dr. H. Rodin and Dr. D. Musgrave.

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## MANHATTAN DERMATOLOGIC SOCIETY

**Wilbert Sachs, M.D., *President***

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***Feb 8, 1949***

**Fordyce's Disease of the Buccal Mucosa, Lips and Penis.** Presented by Dr. Anthony C. Cipollaro.

T. M., a bartender aged 39, first consulted me on Jan. 6, 1949, for treatment of an eruption on the penis of ten months' duration. The patient stated that, initially, tiny blisters and fissures had appeared proximal to the corona. Episodes of "cold sores" recurred at monthly intervals in this area for about six months. There had been persistent erythema in the affected region. The eruption had always been asymptomatic, and the patient denied having had intercourse for one year. He had received roentgen therapy, "autoblood" injections and various other intravenous and intramuscular injections. He had been vaccinated about six times.

The patient presents a diffuse, erythematous band 2 cm. wide involving the distal portion of the shaft of the penis circumferentially. There is fissuring and slight infiltration in the region of the corona. Pinhead-sized, yellowish, maculopapular lesions, discrete and aggregate, are visible in the area of erythema.

Examination of the mouth discloses similar lesions in greater abundance, forming large plaques on the buccal mucosa. There are discrete lesions on the upper lip. A great number of telangiectatic vessels are seen on the superior portion of the buccal mucosa.

The patient is presented because of the rarity of lesions of Fordyce's disease on the penis.

DISCUSSION

DR. NATHAN SOBEL: I agree with the diagnosis. I have never seen a case of Fordyce's disease of the genitals, although I believe a few examples have been reported in the literature.

DR. ANTHONY C. CIPOLLARO: The associated telangiectasia and erythema were unusual to me. We thought of moniliasis and did cultures and scrapings but could find no organisms. However, I think I shall have the areas painted with methylrosaniline chloride when the patient returns for treatment.

**A Case for Diagnosis (Drug Eruption? Acrodermatitis Atrophicans Chronica?).** Presented by DR. GEORGE M. LEWIS and DR. WILBERT SACHS.

T. E., a woman aged 48, is presented from New York Hospital. Approximately one and one-half years before presentation she noted two small erythematous, macular lesions on the left forearm, their appearance following an injury at that site. These changed little until six months before presentation, when for the first time there began to be an extension of the process. The spread was particularly rapid in the preceding three months. The lesions have been entirely asymptomatic throughout this time.

The patient stopped menstruating in August 1948. For about one year she took "hormone injections," and for three months, "hormone pills." Treatment with both of these was stopped in December 1948. Empirin® compound tablets (composed of acetophenetidin, caffeine and acetylsalicylic acid) have been a favorite drug, used from one to seven times weekly for headaches.

She denies having venereal disease. The history is noncontributory.

Along the ulnar border of the left forearm there are several soft, slightly elevated plaques which are faintly erythematous and poorly circumscribed. The overlying skin is dry and shiny and shows a slight suggestion of atrophy, but this condition is also seen elsewhere in apparently normal skin. There is a similar plaque on the dorsal surface of the left hand. Some varicosities are noted on the legs.

Serologic tests for syphilis all gave negative reactions. The hemogram showed 14.2 Gm. of hemoglobin, 5,300,000 red blood cells and 6,000 white blood cells, with 36 lymphocytes, 9 monocytes, 1 eosinophil and 42 mature and 12 band form polymorphonuclear leukocytes.

Biopsy showed the vessels throughout the cutis to be dilated. There was moderate interstitial edema. The epidermis was acanthotic but otherwise showed no important change. The vessel walls were swollen. The intima was swollen, and in places the lumens of the vessels were almost occluded. About the vessels there was a vast focal infiltration composed of plasma cells. In making the diagnosis secondary syphilis should be ruled out.

DISCUSSION

DR. WILBERT SACHS: The section shows all the features of secondary syphilis. Clinically, I would never think of syphilis. All serologic tests gave negative reactions.

DR. NATHAN SOBEL: Syphilis can mimic anything. I have seen cases in which there was a negative reaction to the Mazzini test which was found to be positive on serial dilutions, and so I would suggest that serial dilutions be done and also that a therapeutic test, whether with arsenic and bismuth preparations or with penicillin, be made. If the condition is an inflammatory process, not syphilitic, it will heal on treatment with penicillin anyway. Even with the most sensitive tests we may on rare occasions get a false negative serologic

reaction in a patient with early syphilis, and since the histologic picture is almost specific, I would treat the patient for syphilis.

DR. WILBERT SACHS: Would you have thought of syphilis clinically?

DR. NATHAN SOBEL: No, but I have seen similar eruptions that have turned out to be syphilis.

DR. IAN O. STAHLE, Melbourne, Australia (by invitation): Clinically, I had the impression that there was a faint spreading, serpiginous margin at one site on the forearm. Some areas which are depressed and atrophic are suggestive of the end result of a chronic granulomatous process such as syphilis. The possibility of leprosy should also be considered.

DR. PAUL GROSS: It would be difficult to make a diagnosis on the basis of any lesion on the forearm, but, because of the typical circumscribed acrodermatitis atrophicans chronica, I think the diagnosis should be accepted. However, it is true that there have been cases of tertiary syphilis that terminate in something which resembles acrodermatitis atrophicans chronica, and I therefore think a therapeutic test is indicated.

DR. ORLANDO CANIZARES: At present it is impossible to make a diagnosis. The fact that the patient has acrodermatitis atrophicans chronica is a point in favor of a diagnosis of syphilis, although acrodermatitis atrophicans chronica may be idiopathic or due to other diseases, such as leprosy.

DR. NATHAN SOBEL: I think also that spinal fluid, neurologic, cardiovascular and eyeground examinations should be performed to see whether there is anything to corroborate the diagnosis.

DR. WILBERT SACHS: I could not fit the histologic picture in with tertiary syphilis or leprosy.

**Chronic Benign Familial Pemphigus.** Presented by DR. NATHAN SOBEL.

H. McD., a woman aged 34, registered at the Skin and Cancer Unit in February 1949, complaining of an eruption which had been recurring for the past seven years.

Over the right scapular region there is an irregularly shaped plaque 3 by 2 inches (8 by 5 cm.) in diameter. This is crusted, oozing and erythematous. Around this lesion are scattered several smaller ones. The patient complains of severe pruritus and soreness. This eruption started seven years ago on the right side of the neck, disappeared, and recurred in different areas on the back of the trunk. The duration of these lesions varies from five to ten months. The free periods are from two or three months. The eruption is usually worse in summer and milder in winter. The present lesion started six months ago. The past history of the patient is irrelevant.

One brother and three sisters never had any cutaneous lesions. The father is said to have had an eruption in the axilla which used to recur in warm weather.

Biopsy confirmed the clinical diagnosis.

DISCUSSION

DR. SAMUEL M. PECK: I think we are beginning to have a better idea of the so-called Hailey and Hailey pemphigus. Some of the cases reported as Darier's disease I think are undoubtedly of the type of eruption seen tonight. Whether this condition is synonymous with what Dr. Sachs believes is epidermolysis bullosa, I am not quite ready to state.

DR. MAX SCHEER: Clinically, I would say that this is the Hailey and Hailey disease. The lesions disappear spontaneously, as they often do in that disease, and the location is right. I would accept that diagnosis.

DR. HERMAN SHARLIT: I agree with the diagnosis, but I don't like that name and hope somebody changes it.

DR. ANTHONY C. CIPOLLARO: I accept the diagnosis of Hailey and Hailey's pemphigus, but as I saw that many of the old lesions were really infected excoriations in areas where the patient could reach and scratch, I felt that the condition might be dermatitis artefacta.

DR. NATHAN SOBEL: At the time the biopsy specimen was taken the skin was rubbed rather vigorously with alcohol, and the section showed a pronounced Nikolsky reaction. In this disease lesions develop at the sites of trauma, whether from clothing, scratching or other causes, just as in epidermolysis bullosa. Some of the cases go along misdiagnosed. I saw a patient recently who was treated for many years for recurrent dermatitis of the axillas, and yet on going into the history it was found that the sister and mother have typical Hailey and Hailey's disease.

**Parapsoriasis Treated with Vitamin $D_2$.** Presented by DR. ORLANDO CANIZARES.

E. M., a man aged 24, acquired in May 1947 an eruption manifested by pinhead-sized to pea-sized erythematous macules or maculopapules, some of them covered with an adherent scale. The lesions were profuse on the trunk and also involved the extremities. The patient was seen at the Veterans Administration Hospital on April 9, 1948, and a clinical diagnosis of parapsoriasis (guttate type) was made and confirmed by microscopic examination. The patient was treated with ultraviolet irradiation with little improvement. In August 1948 he went to Florida, where he exposed himself repeatedly to sunlight. The result was an almost complete disappearance of the lesions. Two weeks after his return to New York city the eruption reappeared suddenly. Besides the scales and papules, many vesicular varioliform lesions were preesnt. The diagnosis of pityriasis lichenoides et varioliformes acuta was made.

Vitamin $D_2$ therapy was begun on September 6 in a dosage of 50,000 units three times a day. On September 30 the patient showed complete recovery. No signs of toxicity were noticed.

On November 27, the patient returned, presenting a papulosquamous eruption similar to that observed on the first admission. Vitamin $D_2$ therapy in the same dosage was resumed. After three weeks the lesions had disappeared almost entirely, leaving only residual pigmentation on the upper extremities and some depressed scars on the legs and trunk. Roentgenologic examination of the chest showed no abnormalities. The urine, blood cell counts and blood chemistry, including calcium and urea nitrogen determinations, were all normal. The patient was seen again on Feb. 8, 1949, and showed no evidence of relapse.

**Parapsoriasis Treated with Vitamin $D_2$.** Presented by DR. ORLANDO CANIZARES.

F. P., a man aged 35, was seen at the Veterans Administration Hospital on Nov. 29, 1948. At that time he presented an eruption on the trunk and extremities of two years' duration. The lesions were slightly elevated, erythematous papules covered with thin, adherent scales. They varied in size from a few millimeters to 2 cm. in diameter. On coalescing, the lesions produced a retiform appearance which was most pronounced on the trunk. There were many punctate hemorrhagic lesions irregularly distributed over the affected areas and more numerous on the lower extremities. The diagnosis of parapsoriasis guttata, with some retiform

elements, was made on a clinical basis. Observations on microscopic examination were reported to be consistent with the diagnosis of parapsoriasis.

Treatment with vitamin $D_2$ was begun on November 29, 50,000 units three times a day, and continued up to December 22, when the lesions had cleared up almost completely, only residual pigmentation remaining.

On Jan. 10, 1949 many new lesions had appeared. On that date treatment with vitamin $D_2$ was reinstituted, and a prompt remission of the lesions resulted. On repeated occasions throughout the treatment, results of routine laboratory tests were normal, including determinations of blood calcium and urea nitrogen levels. Roentgenologic examination of the chest showed no abnormality. On February 8 the treatment was discontinued. There was no clinical evidence of toxicity.

DISCUSSION OF CASES OF PARAPSORIASIS

DR. NATHAN SOBEL: I was much impressed with the results and wish to congratulate Dr. Canizares. I shall use this therapy for patients with parapsoriasis.

DR. SAMUEL M. PECK: I have never been able to help any of my patients. I am wondering whether these patients will eventually be maintained on much smaller doses.

DR. HERMAN SHARLIT: This is the first time I have seen such eruptions that came and went. If this experience can be repeated, it might give us an idea of how to go about dealing with the condition.

DR. PAUL GROSS: I was also impressed by the result, but would have to make a reservation in 1 case, that which resembles chronic parapsoriasis varioliformis. In my experience, most of these cases are self limited. Of course, the older man with typical guttate parapsoriasis also had a response. I should not care to use this treatment for parapsoriasis because of the inherent danger.

DR. ANTHONY C. CIPOLLARO: It is a wonderful demonstration of a therapeutic result, and I shall go right on treating patients with vitamin $D_2$, giving 150,000 to 200,000 units daily without fear. I think that the response in all patients I have treated so far and those I have read about indicates that vitamin $D_2$ is a fairly safe drug when given in reasonable doses.

DR. ORLANDO CANIZARES: This treatment was originated by the staff at the Veterans Administration Hospital. To answer Dr. Gross, both the guttate and the varioliform type respond to therapy. The second patient is still in the hospital. We are trying to reach a maintenance dose. As to the toxicity, 1 of our patients had moderate nausea. The patients should be kept under medical observation. These are the first 2 patients on whom we have used this therapy, but we hope to continue the study of the effects of vitamin $D_2$ in parapsoriasis.

**Systemic Coccidioidomycosis.** Presented by DR. ORLANDO CANIZARES.

W. F., a Negro aged 39, is presented from Bellevue Hospital complaining of a granulomatous mass 10 mm. in diameter at the distal end of a scar 3 mm. long on the left palm.

The patient lived in the San Joaquin Valley, California, during 1939. Two years later he noticed a swelling of the ulnar side of the left hand. This was incised but did not heal. The patient was seen at Sea View Hospital, Staten Island, N. Y., where the diagnosis of tuberculosis was made. Roentgenograms showed destruction of the fifth metacarpal bone. As a result the fifth finger of the involved hand was amputated.

In September 1948 the patient lost weight and acquired a cough. Roentgenograms of the chest revealed diffuse infiltration involving the major portion of the upper lobe of the right lung, which was diagnosed as chronic productive tuberculosis. The left lung was normal. However, repeated smears and cultures of the sputum revealed no acid-fast organisms.

In August 1948 the patient noticed a mass in the palm of the left hand, which was removed surgically on December 2. Two sinuses were found beneath the skin, and these were probed down to the muscular layer. Histologic examination of specimens taken at this time showed hyperkeratosis of the squamous epithelium. At one point the epithelium was discontinuous and the defect was filled in by granulation tissue in which were observed fairly discrete epithelioid tubercles, some of which had necrotic centers containing polymorphonuclear cells and about which numerous giant cells of the Langhans type were seen. In one giant cell a large (50 microns) sporelike structure was seen with a doubly contoured wall and a granular blue center. The Ziehl-Neelsen stain revealed several more spores but no acid-fast bacilli.

The skin test with coccidioidin gave positive reactions in a dilution of 1:10. With only rest in bed and symptomatic medication the patient's pulmonary manifestations of the disease improved rapidly. The latest roentgenologic examination of the chest showed completely normal fields.

DISCUSSION

DR. HERMAN SHARLIT: Is surgical excision an effective treatment? It is a quick way to get rid of the lesion, but I thought the theory was that with it one always left some infection behind which started up again.

DR. WILBERT SACHS: Do I understand that the diagnosis rests on the finding of that one organism? The positive reaction to the coccidioidin test does not mean much, because it is positive in most persons from that area.

DR. ORLANDO CANIZARES: The diagnosis of tuberculosis was made when the finger was amputated. At Bellevue we thought of the possibility of coccidioidomycosis because the patient had been in the San Joaquin Valley. The intradermal test was positive, and the organisms were seen in the slide, which observation is definite proof. While I was in the Army, stationed in Arizona, I saw several cases of the disseminate type. The lesions presented by this patient probably started in the bone; a sinus formed, and then the skin became affected. Forbes (*Mil. Surgeon* **99**:653 [Nov.] 1946) stated that many of the soldiers who have been in the San Joaquin area might have contracted the primary infection there and that from a flare-up of those lesions disseminated ones may appear.

DR. ARTHUR B. KERN (by invitation): The diagnosis of cutaneous coccidioidomycosis has been established by demonstration in the biopsy section of double-walled spherules containing endospores characteristic of Coccidioides immitis. The nature of the pulmonary disease has not been as definitely determined, since repeated smears and cultures of the sputum have failed to reveal either acid-fast bacilli or spores of C. immitis. However, the serial roentgenograms of the patient's chest show resolution of the disease process much too rapid for tuberculosis and yet too slow for bronchopneumonia or pneumonitis. Therefore, in view of the evidence of cutaneous coccidioidomycosis, I believe that we can correctly assume that the pulmonary changes are also due to C. immitis.

**A Case for Diagnosis (Panniculitis? Lymphogranuloma Benignum?).** Presented by DR. MAX SCHEER.

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***Feb. 9, 1949***

**Hereditary Hemorrhagic Telangiectasia.** Presented by DR. CHESTER N. FRAZIER, Boston.

J. S., a 54 year old white man of Syrian birth, gave a history of repeated attacks of epistaxis of varying grades of severity for twenty-six years. Two years after the onset of epistaxis, vascular lesions first appeared on the face. These slowly increased in number and in size. The patient's mother had similar lesions and repeated nasal hemorrhages. No other member of the family was known to be affected. Between 1925 and 1949 the patient had been treated many times for epistaxis. Hemorrhage was so profuse on several occasions as to require repeated blood transfusions. Bleeding was observed only from the nasal cavity.

Examination reveals many telangiectases and multiple hemangiomas on the patient's face, with the malar regions most profusely affected. The angiomas are as large as 6 to 8 mm. in diameter and elevated from 1 to 3 mm. There are also numerous telangiectatic excrescences on the nasal mucosa, affecting the septum, turbinates and floor of the nose. Similar lesions and small hemangiomas may also be seen on the tongue and on the buccal and pharyngeal mucosa. Aside from these vascular lesions, a complete physical examination discloses no demonstrable abnormality.

The bleeding, clotting and prothrombin time were normal. After a recent hemorrhage the red blood cell count was 3,400,000 per cubic millimeter, and the hemoglobin, 6.6 Gm. per hundred cubic centimeters. Hemorrhages have been arrested by tampons and by electrocauterization of the bleeding points. Between 1932 and 1937 the patient received approximately 3,000 r of high voltage roentgen therapy (200 kilovolts) to each side of the face and nose, but without appreciable effect on the lesions. In 1941 a right lateral rhinotomy was performed. Hemorrhages continued, and new lesions appeared on the face. In December 1948, 300 r of roentgen radiation (200 kilovolts) was given to each of three areas, namely, the anterior, left and right portions of the nasopharynx; in January 1949 another 200 r was administered. In each instance one area was treated on each of three consecutive days. The last serious nasal hemorrhage was in February 1949.

### DISCUSSION

DR. CHESTER N. FRAZIER, Boston: It has long been known that hemorrhagic telangiectasia is familial. The dyscrasia is assumed to be a genetic trait dependent on a dominant hereditary factor. Both sexes are equally affected. In all, about 1,000 cases in 150 families have been reported. Recently Snyder and Doan (Studies in Human Inheritance: XXV. Is the Homozygous Form of Multiple Telangiectasia Lethal? *J. Lab. & Clin. Med.* **29**:1211 [Dec.] 1944) reported a case which may throw additional light on the genetics of this disease. According to these observers, among all the previously reported cases none had occurred in a person both of whose parents had the disease. In the patient they described, both parents had hemorrhagic telangiectasia, as also did one of the paternal and one of the maternal ancestors. In the offspring the result was fatal. The infant was born with extensive telangiectases of the skin and mucous membranes and died at 11 weeks of age.

All the visceral organs showed multiple hemangiomas and hemorrhages. If a gene is completely dominant, it produces the same effect when it is inherited through one parent, that is to say, a heterozygous form of hemorrhagic telangiectasia. If this contention should be true, its consideration would be of importance in the contemplated marriage of two persons both of whom have the disease.

DR. FRANCIS P. MCCARTHY, Boston: I observed a case about ten years ago similar to the one this man has but with much less involvement. The patient bled from the nares and from his tongue, but the lesions on the face were relatively mild. The nares were electrodesiccated rather thoroughly and the tongue treated with electrocoagulation and radium. The nasal hemorrhages were controlled and the tongue lesions improved. The patient had a son about 20 years of age, who had about the same degree of facial involvement. Cerebral symptoms developed, and there was blood in the spinal fluid; a diagnosis of probable cerebral hemangioma was made.

DR. CHESTER N. FRAZIER, Boston: It is important to know that other vascular anomalies may occur; lesions of the cerebral and splenic arteries have been observed Aneurysms may form and rupture at times. Lesions have been found along the gastrointestinal tract as far down as the duodenum. It is possible that pulmonary vascular abnormalities occur in some cases.

**A Case for Diagnosis (Benign Pemphigus of the Mucous Membrane?).** Presented by DR. WALTER F. LEVER, Boston.

E. M. M., a 60 year old white woman, a retired school teacher, presents lesions of the mouth, conjunctivas and vagina of twenty-six years' duration. She stated that painful erosions followed by scars had been developing in these areas at irregular intervals. There had been difficulty in swallowing for twenty years, but never any hoarseness. About ten years ago there was an eruption on the sides of the neck which was diagnosed as lichen planus after the removal of a biopsy specimen. This eruption disappeared within a few months' time. For the ten years before presentation there have been occasional nontender nodular lesions on the lips which have been removed from time to time by electrodesiccation. The patient's younger sister has had an apparently similar oral and vaginal condition for the previous three years.

Examination discloses a woman of stated age who appears healthy and in no obvious distress. The most obvious changes are noted on her lips, which are covered with a layer of exuberant crusting that is 5 to 6 mm. thick. This encrustation has a firm, almost verrucous or vegetative character and extends to the vermilion borders of the lips. It is not tender when palpated. The vegetations cease on the gingival aspects of the lips, but on them there are scattered shallow erosions. The gingival, buccal and conjunctival mucosae exhibit similar small, denuded areas. There is also scarring in the lower fornices of the conjunctivas and the buccal mucosa. Vegetations and scars limit opening of the mouth. Similar scarring is notable on the vaginal mucosa, and the introitus is so contracted as to admit but one finger.

A biopsy specimen removed from a nodule on the upper lip in December 1943 was reported to reveal squamous cell carcinoma. Other specimens of lip lesions were said to exhibit only chronic inflammation or lichen planus. The patient stated that she had received gold and sodium thiosulfate injections some years ago without benefit. No other treatment was reported. In June of 1946 an esophagoscopy was performed and revealed stenosis in the upper part of the thoracic portion of the esophagus with submucous infiltration. No ulceration was seen.

DISCUSSION

DR. FRANCIS P. MCCARTHY, Boston: Since the extraction of all her teeth two years ago, this woman's oral condition has been worse. The tongue is smooth, with atrophy of the filiform papillae resembling the "bald" tongue of late syphilis. The chronicity of this oral disease could ultimately produce vegetating lesions as seen in this case, owing to chronic irritation and secondary infection. I do not believe that the condition is lichen planus, although the bullous type may assume some degree of chronicity. In spite of the microscopic picture suggesting lichen planus, it might be added that other chronic oral mucosal lesions may produce a cellular reaction similar to the one in that disorder. I favor the diagnosis of benign oral pemphigus with a secondary nonspecific vegetating reaction.

DR. WALTER F. LEVER, Boston: I am glad to get some support for the diagnosis of benign pemphigus of the mucous membranes. In making this diagnosis we can at least reassure the patient that the nodules on her lips are not cancerous.

DR. FRANCIS M. THURMON, Boston: Has anyone seen cancer developing in the cicatrices of benign pemphigus of the mucous membranes?

DR. WALTER F. LEVER, Boston: Dr. Fred Weidman examined the sections but did not definitely commit himself.

DR. G. MARSHALL CRAWFORD, Brookline, Mass.: Have you examined this woman completely as far as the integument is concerned?

DR. WALTER F. LEVER, Boston: The patient has pronounced shrinking of the vaginal introitus. There is hard atrophic scar tissue in the vagina.

DR. G. MARSHALL CRAWFORD, Brookline, Mass.: That description sounds like kraurosis.

DR. WALTER F. LEVER, Boston: There is too much inflammatory activity. I considered kraurosis as well as lichen sclerosus et atrophicus and lichen planus. In the vagina the lesions are limited to the mucous membrane. They do not extend to the cutaneous portion of the vulva.

DR. G. MARSHALL CRAWFORD, Brookline, Mass.: Have you obtained a biopsy specimen from that region, and have you checked for possible secondary monilial infection of the mouth?

DR. WALTER F. LEVER, Boston: No.

DR. FRANCIS P. MCCARTHY, Boston: Have you examined the esophagus since 1946?

DR. WALTER F. LEVER, Boston: This patient has multiple strictures of the esophagus. Their presence is in favor of a diagnosis of benign pemphigus of the mucous membranes. I have had 2 patients myself with esophageal lesions and know of 1 patient with benign pemphigus of the mucous membranes who acquired complete stenosis of the esophagus and died of it.

DR. LEON BABALIAN, Portland, Maine: Would you consider acetarsone therapy?

DR. WALTER F. LEVER, Boston: I have not treated the patient. She has had numerous injections of gold preparations. I want to be more certain of the diagnosis before instituting any treatment. My experience with therapy of this disease has been distressing. I have given some patients arsenic, but I think it is worthless for the condition.

DR. G. MARSHALL CRAWFORD, Brookline, Mass.: A diagnosis of Behcet's disease might be considered in this case.

**Scleredema Adultorum.** Presented by DR. GEORGE E. MORRIS, Boston.

P. M., a 10 year old white boy of Greek birth, presents swelling of the face and neck of twelve days' duration. The patient acquired a felon on the left index finger about three weeks previously; this was incised and drained. Two weeks before presentation he acquired an acute infection of the upper respiratory tract. A few days later he complained of soreness and stiffness of the neck. It became swollen rather rapidly and was soft at first but has gradually become hard with a pronounced feeling of tightness. There is some pain in the neck, especially at night.

Examination of the urine revealed no sugar, but there was a 1 + reaction for albumin; the $p_H$ was 5.5, and the urinary sediment contained occasional white blood cells. The hemoglobin content of the blood was 15 Gm. The erythrocytes of the blood numbered 5,700,000, and the leukocytes, 10,050 per cubic millimeter. A blood smear displayed 64 polymorphonuclear leukocytes, 33 lymphocytes, 2 eosinophils and 1 monocyte; the red cells and platelets appeared normal. A hematocrit reading was 45. The sedimentation rate was 5 mm. in one hour.

Treatment had consisted of the administration of "amino acids" by mouth.

DISCUSSION

DR. WALTER F. LEVER, Boston: I am interested in the histopathologic changes. There is some argument in the literature as to what material is deposited in the collagen to cause the edema. Freund (Ueber Sklerodema [Buschke], *Arch. f. Dermat. u. Syph.* **161**:92, 1930), in working with stains, claimed that with cresyl violet the material stained faintly pink, like mucin. Vallee (Scleredema, a Systemic Disease, *New England J. Med.* **235**:207, 1946) recently reported 2 cases of Buschke's disease; in 1 he obtained staining reactions suggesting the presence of mucin. Since the disease is rare, I think it would be worth while to perform a biopsy, use alcohol as a fixative and stain sections with Best's mucocarmine and with cresyl violet.

DR. LEON BABALIAN, Portland, Maine: I should like to know whether the change in the collagen of scleredema adultorum disclosed by mucocarmine stain is the same as is found in localized myxedema and whether its meaning is the same in both instances.

DR. WALTER F. LEVER, Boston: As a rule, yes. The mucin in myxedema stains much more readily and can usually be recognized as such in routinely stained sections.

DR. FRANCIS P. MCCARTHY, Boston: What is the course of the disease?

DR. G. MARSHALL CRAWFORD, Brookline, Mass.: Most patients will be well in three to six months without therapy.

DR. PAUL J. CATINELLA, Boston: I have seen 1 case last as long as eight years. In this instance I should think the condition will improve rather rapidly.

DR. NEVILLE KIRSCH, Hartford, Conn.: One of the opinions in regard to the etiology of this disorder indicated an infectious nature in that the condition apparently followed streptococcic or influenzal diseases. Wise (ARCH. DERMAT. & SYPH. **56**:276 [Aug.] 544 [Oct.] 1947) used penicillin in a case like this and obtained complete involution. The prognosis in most cases is good, since the condition disappears spontaneously.

**Tumor of the Right Shin in a 71 Year Old Man (Lymphosarcoma or Reticulum Cell Sarcoma?).** Presented by DR. GEORGE E. MORRIS, Boston, and (by invitation) DR. LOUIS KROGER, Fall River, Mass.

J. T. K., a 71 year old white man, presents a lesion on his right shin of one year's duration. This began as a small asymptomatic tumor which gradually enlarged, and others have developed around it. The patient has felt entirely well during this time. He has lost no weight.

On examination the patient appears to be in good health. At about the junction of the middle and lower thirds of the anterior aspect of the right leg there is a group of purplish red tumors, rather closely clustered together and partially coalesced. The individual nodes vary in size from 1.5 to 7.5 cm. in diameter; the largest is elevated to a height of approximately 1.5 cm. Some of the smaller peripheral lesions are discretely separated from the larger fused central mass. They are all decidedly hard to palpation. No enlargement of the popliteal or inguinal lymph nodes can be detected.

Roentgenologic examination of the chest showed normal conditions. The hemoglobin content of the blood was 82 per cent. The erythrocytes of the blood numbered 4,390,000, and the leukocytes, 12,750 per cubic millimeter. A blood smear disclosed a normal differential count. Histologic examination of a biopsy specimen revealed that "the epidermal layer was slightly thinned; there was a diffuse infiltrate of small round cells, and some areas revealed multiple, large, pale-staining blue cells, some of which exhibited mitotic figures." No therapy had been administered.

DISCUSSION

DR. WALTER F. LEVER, Boston: I wish to point out that Gall and Mallory (Malignant Lymphoma, *Am. J. Path.* **18**:381, 1942) reported 618 cases of lymphoma from the Massachusetts General Hospital. They pointed out that one third of the stem cell lymphomas and reticulum cell lymphomas started out as single lesions and remained localized for some time. Follow-up showed that if there was adequate destruction of the lymphoma many of those patients actually were cured. Everything should be done to eradicate the lymphoma completely in this case. The patient will then have a good chance to survive. I think the surgeons should decide whether or not to amputate the leg. I would not rely on the use of urethane. My preference would be for wide surgical excision of the lesions plus treatment with urethane.

DR. FRANCIS P. MCCARTHY, Boston: I have the impression that this disease is not localized to the leg. Primary lesions said to be of lymphomatous origin starting in the skin do not fit in with my conception of lymphoma. This man probably has involvement of lymph nodes somewhere in the body, and the lesions of the leg probably are a cutaneous manifestation of a primary condition elsewhere. I cannot recall an amputation performed for a lymphomatous lesion.

**Sickle Cell Anemia with Ulcers of the Leg.** Presented by DR. GEORGE E. MORRIS, Boston.

**Urticaria from Physical Factors.** Presented by DR. JOHN G. DOWNING, Boston.

**Alopecia Areata.** Presented by DR. FRANCIS M. THURMON, Boston.

**Urticaria Pigmentosa.** Presented by DR. JOSEPH GOODMAN, Boston.

**A Case for Diagnosis (Dermatitis Herpetiformis or Benign Pemphigus of the Mucous Membranes?).** Presented by DR. WALTER F. LEVER, Boston.

**Dermatitis Due to Undetermined Cause.** Presented by DR. AUSTIN W. CHEEVER, Boston.

**Poikiloderma Vasculare Atrophicans (?).** Presented by DR. WALTER F. LEVER and DR. ARTHUR S. SPANGLER, Boston.

**A Case for Diagnosis (Melanosis, Occupational or Toxic?).** Presented by DR. GEORGE SCHWARTZ, Malden, Mass.

**Occupational Calluses in a 10 Year Old Tumbler.** Presented by DR. G. MARSHALL CRAWFORD, Brookline, Mass.

**Lymphangioma Circumscriptum.** Presented by DR. PAUL J. CATINELLA, Boston.

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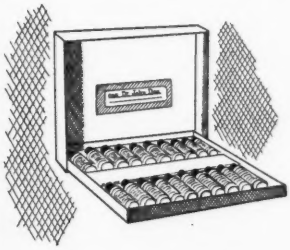

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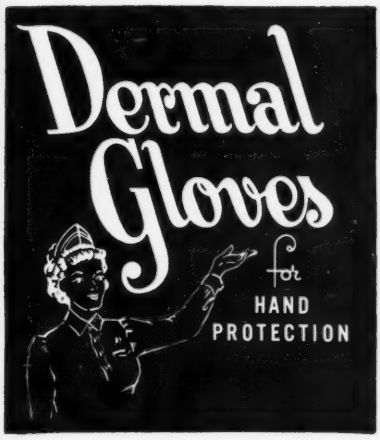


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